

**National Advisory Committee (NAC)
for Acute Exposure Guideline Levels (AEGLs) for Hazardous Substances**

March 7-8, 2003

Final Meeting-28 Highlights

Eagle Gate East & West
Best Western Salt Lake Plaza Hotel
122 West South Temple
Salt Lake City, Utah 84101

INTRODUCTION

George Rusch, NAC/AEGL Chair, opened the meeting with brief remarks noting that this off-site meeting was in conjunction with the 42nd Annual Meeting of the Society of Toxicology. At the end of the meeting, George surveyed the committee members regarding their opinion on having the regular quarterly NAC/AEGL meetings in conjunction with other meetings such as SOT. EPA staff scientists, George Woodall and Marquee King, were introduced. George noted the absence of Roger Garrett, AEGL Program Director, due to illness.

Paul Tobin provided an update from EPA on the use of data involving human subjects for development of AEGL values (Attachment 1). In addition, Ernie Falke referred to the Standing Operation Procedures (SOPs) for a statement on human studies. The SOPs state that no data on humans known to be obtained through force, coercion, misrepresentation or any other such means will be used in the development of AEGLs (Attachment 2).

Paul Tobin reported that an internal AEGL web site is under development and will be maintained by Po-Yung Lu. In the near future, draft TSDs and key references will be available on the web site prior to NAC/AEGL meetings. Ursula Gundert-Remy mentioned that the Europe ACUTEX is making good progress and will keep the NAC/AEGL updated in the future.

The draft NAC/AEGL-27 meeting highlights were reviewed; two minor changes were suggested. John Morawetz asked for clarification on whether the meeting had discussed if the health effects found in toluene studies below 200 ppm were considered AEGL 1 effects. He also was concerned about how the committee should proceed if a member raises a question on the accuracy of the description of a paper used in the TSD section on the derivation of AEGL values. He proposed that the committee either reach a consensus on the description of the paper or postpone discussion on the derivation section and withhold judgment until there is a consensus. A motion was made by Mark McClanahan and seconded by John Hinz to accept the meeting highlights as presented with the aforementioned revisions. The motion passed unanimously by a voice vote.

The final version of the NAC/AEGL-27 meeting highlights is attached (Appendix A) and was distributed to the NAC/AEGL by e-mail on March 28, 2003.

The highlights of the NAC/AEGL-28 meeting are summarized below along with the Meeting Agenda (Attachment 3) and the Attendee List (Attachment 4). The subject categories of the highlights do not necessarily follow the order listed in the NAC/AEGL-28 Agenda.

STATUS REPORTS

NRC/COT/AEGL Subcommittee Review Meeting of January 27-29, 2003

Ernie Falke reported that a total of 13 (new and revisited) TSDs were reviewed in January at Irvine, CA. They are Acrylic acid, Allylamine, Carbon monoxide, Chlorine dioxide, Crotonaldehyde, Cyclohexylamine, Ethylenediamine, Ethyleneimine, HFE-7100, Hydrogen sulfide, Methanol, Phenol, and Propyleneimine. In addition to reviewing the TSDs, the concept of LOA was introduced to COT/AEGL subcommittee. The COT/AEGL supported the concept of LOAs. LOA methodology will be incorporated into the SOPs in the near future.

Critical Health Effects Starting Points for AEGL Determination: LOAEL vs NOAEL

Roger Garrett and George Alexeeff had a number of discussions on the TSDs of concern. A summary status report (Attachment 5) was prepared by Po-Yung Lu and distributed to the NAC/AEGL for information and any further discussion. It appeared that no more clarification is warranted and a motion was made by George Alexeeff and seconded by Bill Bress to accept the status report. The motion was approved by a unanimous voice vote (Appendix B).

TECHNICAL ISSUE DISCUSSIONS

LOA Subcommittee Report: Data Quality Report Mark McClanahan

Mark McClanahan summarized the odor subcommittee's February 13, 2003 conference call. George Alexeeff discussed three tables he had developed showing chemical specific sub-AEGL-1, AEGL-1 and AEGL-2 signs/symptoms identified in the TSDs. Most of the discussion focused on the AEGL-1 table. The AEGL-1 table includes those signs/symptoms used to define the AEGL-1 level as well as those classified as more severe than AEGL-1 but not AEGL-2 signs/symptoms. The participants expressed some confusion with the AEGL-1 table. George Alexeeff will revise the AEGL-1 signs/symptoms table. He may produce two separate tables or designate those signs/symptoms which have not been used to define AEGL-1 but have been identified in the TSDs as below AEGL-2 with an asterisk. George Alexeeff will revise this table and present all three tables at the June meeting. He will also produce a more compact set of

tables (not chemical specific) with just signs/symptoms for these three levels: less than AEGL-1, AEGL-1 (but less than AEGL-2) and AEGL-2.

The subcommittee also discussed a paper about NOAELs/LOAELs published by George Alexeeff that led to the suggestion that George present his findings at the June meeting. With approval of the NAC/AEGL a description of George's findings along with how the NAC/AEGL will use this information will be placed in the SOPs.

Overview of Fundamental Principles of Industrial Hygiene **John Morawetz**

John Morawetz gave a presentation on Basic Occupational Exposure Assessment, noting the variability in exposures in the work environment, the different types of occupational samples and collection devices, and the variable sampling times. He compared the constant exposure to all subjects in animal and human chamber studies to the variability in occupational exposures, the basic sources of occupational variation, and the various types of exposure measurements (area, personal, short-term, time-weighted-averages, bulk) (Attachment 6). He then presented a draft proposal for the evaluation of human exposure measurements in the occupational setting (Attachment 7). The committee agreed with the first two points of his proposal that breathing zone samples are preferable and that the type of sample should be clearly described in the TSD (Appendix C). Discussions on the rest of John Morawetz's proposal was deferred to the June meeting when Ed Bishop of the NRC/COT will be attending. A working team was formed to explore these issues further.

AEGL Applications: Relevance to Occupational Exposures **George Rusch**

A revised draft of the application of Acute Exposure Guideline Levels was distributed at the meeting (Attachment 8) representing input from several committee members. It was briefly discussed before the decision was made to defer further discussion to the NAC/AEGL-29 meeting.

Iron pentacarbonyl **CAS Reg. No. 75-55-8**

Chemical Manager: Ernie Falke, EPA
Staff Scientist: Bob Young, ORNL

Ernie Falke reviewed the values that were originally approved by the NAC/AEGL in NAC/AEGL-25 (June 2002) (Attachment 9). The point-of-departure (POD) for the AEGL-3 was 2.91 ppm for 6 hours which resulted in the death of 1/10 rats (a second exposure resulted in 50% mortality). The NAC/AEGL decided to revisit the AEGL-3 because it was based on a "LOAEL."

There was uncertainty as to how many deaths actually resulted from the single exposure as deaths may not occur for several days. Ernie did a benchmark dose analysis (log probit) of the BASF (1995) rat data using two scenarios: 1 of 10 or 5 of 10 animals would have died from the exposure to 2.91 ppm. Assuming 1/10 deaths, the resulting MLE LC₀₁ and BMDL LC₀₅ were 2.4 and 1.7 ppm, respectively. Assuming 5/10 deaths, the resulting respective values were 1.9 and 0.80 ppm (Attachment 9). Normally the more conservative BMDL LC₀₅ of 0.80 ppm would apply. However, no deaths occurred when 10 rats were exposed to 1.0 ppm for 6 hours/day for up to 28 days. Therefore, 1.0 ppm was chosen as a more reasonable POD. Because the rat is 2-3 times more sensitive than the mouse (based on the data of Sundeman et al. 1959) and a very conservative endpoint was used (no deaths for 28 days), an interspecies uncertainty factor of 1 is reasonable. An intraspecies uncertainty factor of 3 as used in the original derivation was retained. Time-scaling utilized n = 1. Steve Barbee noted that the Sundeman et al. (1959) experiment was for only 5 days, a more reasonable acute exposure (the data involved an exposure to 118 ppm and a suggested total UF of 30). It was decided to use the Sundeman et al. (1959) data for support. It was moved Loren Koller and seconded by Mark McClanahan to accept the rederived AEGL-3 values of 3.6, 1.2, 0.60, 0.15, and 0.075 ppm. The motion passed unanimously (YES: 18; NO: 0; Abstain: 0) (Appendix D). There was comment about the 8-hour AEGL-3 value being lower than the ACGIH-TLV.

The original AEGL-2 values were calculated by dividing the AEGL-3 values by 3 (supported by the steep dose-response curve). Tom Hornshaw suggested a larger factor such as 6, based on the 3 for the steep dose-response curve and 2 for bad data. He also suggested looking at nickel carbonyl to derive a structure-activity relationship. The discussion was tabled at this point. When the discussion was resumed, the consensus was that nickel carbonyl was not a good surrogate for iron pentacarbonyl (this included differences in species sensitivity). It was moved by Bob Benson and seconded by Bob Snyder to retain the original AEGL-2 values. The motion passed (YES:15; NO: 0; Abstain: 1) (Appendix E). It was noted that the reduction factor of 3 must be justified.

REVIEW AND RESOLUTION OF COT/AEGL COMMENTS

Ethyleneimine
CAS Reg. No. 107-15-3
&
Propylenimine
CAS Reg. No. 75-55-8

Chemical Manager: Mark McClanahan, CDC
Staff Scientist: Kowetha Davidson, ORNL

TSDs of Ethyleneimine and Propylenimine were reviewed by COT/AEGL in January 2003. They were approved by COT/AEGL pending the availability of data to develop an LOA. Kowetha Davidson presented the available odor information (Attachment 10) used to develop LOA values

for these two chemicals. Marc Ruijten provided the calculation of the LOA based upon an odor threshold (OT_{50}) for ethyleneimine of 0.698 ppm. This gave an LOA, under field conditions, of 10.8891 which to two figures is 11 ppm. The 10 and 90 percent population response estimates are 2.1 to 56 ppm, respectively. (Under laboratory conditions the default values gives a factor of 12 times the OT_{50} while under field conditions the factor is 16.) A motioned was made by Ernie Falke to accept the LOA of 11 ppm; the motion was seconded by Richard Thomas. The motion passed (YES: 16; NO: 0; Abstain: 1) (Appendix F).

There are no odor threshold data for propylenimine so an LOA value could not be calculated.

Piperidine
CAS Reg. No. 110-89-4

Chemical Manager: Mark McClanahan, CDC
Staff Scientist: Kowetha Davidson, ORNL

The NAC/AEGL committee initially considered piperidine at the June 1997 meeting at which time there was insufficient data on which to base development of either AEGL-2 or AEGL-3 values. Since that time, BASF has made available two studies upon which to base AEGL values. A motion was proposed by John Hinz and seconded by Nancy Kim to set aside AEGL-1 values developed in Sept. 1998. The motioned was unanimously approved (Appendix G). Kowetha Davidson presented data analyses of the two studies (Attachment 11).

The AEGL-1 values were based on the lowest concentration (50 ppm) that caused nasal irritation in rats (nasal secretions and bloody encrustation) during and after a 6-hour exposure; there was no eye irritation at this concentration (BASF, 1990). Uncertainty factors (UF) of 3 for interspecies sensitivity and 3 for intraspecies variability (total UF = 10) were applied to the 50-ppm exposure. The rationale for selecting interspecies and intraspecies UFs of 3 is as follows: (1) the effect observed at 50 ppm was mediated by direct contact of piperidine (corrosive agent) with the nasal epithelium without involvement of other regions of the respiratory tract, and (2) the composition of the nasal mucosa is similar among species and among individuals within the population. After applying a total uncertainty factor of 10, the resulting value of 5 ppm was time scaled based on ten Berge's equation, $C^n \times t = k$. Scaling was based on regression of LC_{50} values for the mouse, guinea pig, and rat ($n = 1.5$). The 6-hour exposure was scaled to other time points except that the 30-minute value was retained for 10 minutes. It was proposed by Bob Snyder and seconded by Bob Benson to adopt the proposed AEGL-1 of 10, 10, 6.6, 2.6, and 1.7 ppm for 10-, 30-minutes, 1-, 4- and 8-hours, respectively. The motion passed (YES:14; NO:1; Abstain:0) (Appendix G).

The initially proposed AEGL-2 values were based on the concentration of piperidine (200 ppm) that caused nasal irritation along with salivation and evidence of some eye irritation within a 6-hour exposure duration. This value was considered a NOAEL for severe irritation. Uncertainty factors and the time scaling procedure were the same as described for derivation of AEGL-1 values. The 30-minute value was retained for 10 minutes because of scaling from a 6-hour exposure. It was proposed by Bob Snyder and seconded by John Hinz to adopt the proposed

AEGL-2 of 100, 100, 66, 26 and 17 ppm for 10-, 30-minutes, 1-, 4- and 8-hours, respectively. The motion failed (YES:8; NO: 6; Abstain:1) (Appendix G). A new endpoint was considered in which the AEGL-2 values were based on the concentration (100 ppm) of piperidine that had no effect on CNS, but caused some irritation (nasal crusts) within a 6-hour exposure duration. Uncertainty factors and the time-scaling procedure were the same as described for derivation of AEGL-1 values. A motion was made by Richard Thomas and seconded by John Hinz to accept the new set of AEGL-2 values: 50, 50, 33, 13, and 8.3 for 10 and 30 minutes and 1, 4 and 8 hours, respectively. The motion passed (YES:11; NO: 2; Abstain:2) (Appendix G).

The AEGL-3 values were based on the LC_{01} calculated from 4-hour lethality data in rats. The LC_{01} of 448 ppm for a 4-hour exposure is lower than the lowest concentration that caused one death among 20 rats (5% lethality) and higher than the concentration that caused no deaths or clinical signs indicative of death. Uncertainty factors of 3 for interspecies sensitivity and 3 for intraspecies variability (total UF = 10) were applied to the LC_{01} . The data for comparing species sensitivity to lethal concentrations of piperidine are very scarce. The reported LC_{50} values for 4-hour exposures was 5996 mg/m³ for the mouse and 4800 mg/m³ for the rat, which is only 20% lower than that for the mouse. These data support an uncertainty factor for interspecies sensitivity of 3. The uncertainty factor for intraspecies variability is 3, because an uncertainty factor of 10 would produce AEGL values for 1, 4, and 8 hours lower than the irritation threshold of 26 ppm. The time scaling procedure was the same as described for AEGL-1. It was proposed by George Alexeeff and seconded by John Hinz to adopt the proposed AEGL-3 values of 370, 180, 110, 45, and 28 ppm for 10 and 30-minutes and 1, 4 and 8 hours, respectively. The motion carried (YES:13; NO: 0; Abstain: 2) (Appendix G).

Proposed AEGL Values for Piperidine (ppm)						
Classification	10 minutes	30 minutes	1 hour	4 hours	8 hours	Endpoint/ Reference
AEGL-1 (Nondisabling)	10	10	6.6	2.6	1.7	nasal irritation/ BASF, 1990
AEGL-2 (Disabling)	50	50	33	13	8.3	nasal irritation, signs of eye irritation, salivation /BASF, 1990
AEGL-3 (Lethal)	370	180	110	45	28	threshold for lethality/ BASF, 1980

The level of distinct odor awareness under field conditions (LOA) for piperidine, based on an OT_{50} of 0.37 ppm is 5.7775 or 5.8 ppm and the estimated 10 and 90 percent population response values are 1.127 or 1.1 ppm and 29.6176 or 30 ppm. A motion was made by Richard Thomas and seconded by Nancy Kim to accept this value and population response estimates for piperidine. The motion carried (YES:12; NO: 1; Abstain:2) (Appendix G).

REVIEW of PRIORITY CHEMICALS

Carbon Disulfide
CAS Reg. No. 75-15-0

Chemical Manager: George Rodgers, AAPCC
Staff Scientist: Jens-Uwe Voss, Germany

The chemical review on carbon disulfide (CS₂) was presented by Jens-Uwe Voss (Attachment 12). AEGL-1 and AEGL-3 values had already been derived in September 2002 (NAC/AEGL-26). The derivation of AEGL-3 was based on data from a study (Du Pont 1966) that was available from secondary sources at that time. Therefore, it was noted at the meeting that the original study is necessary to check the acceptability of the data. The original study was provided by Du Pont and the acceptability was confirmed.

With respect to possible AEGL-2 relevance, effects on the central nervous system (CNS) and effects on the developing embryo/fetus were discussed. Developmental effects (malformations) were observed in animal studies with repeated administration of carbon disulfide for at least one third of the whole gestational period, but no developmental toxicity study with a single exposure was available. The data base was inconsistent as effects reported in Yang et al. 1993 (abstract) and in Tabacova et al. 1978 were not seen in several other studies at higher exposure levels (e.g. Saillenfait et al. 1989). Carbon disulfide reacts with the NH₂-group of endogenous compounds (e.g., amino acids) forming dithiocarbamates. Since some dithiocarbamate chemicals are reproductive and/or developmental toxins in animals, it was discussed whether endogenously formed dithiocarbamates could play a role in the occurrence of developmental effects following carbon disulfide exposure. Although this cannot be ruled out, it has to be taken into account that while carbon disulfide itself is rapidly eliminated from the body after ceasing exposure, the so-called "acid-labile" pool of bound carbon disulfide containing thiocarbamates has a long half-life and increases with daily repeated exposures. Therefore, it is unclear whether developmental effects observed after repeated exposure to carbon disulfide are of relevance for single acute exposures. For the reasons noted above, it was agreed that developmental effects should not be used for the derivation of AEGL-2 values for carbon disulfide.

Regarding effects on the CNS, a single exposure of rats for 4 hours to 2000 ppm led to an inhibition of the escape response (pole climbing in response to a buzzer to avoid electrical shock); no such effect was seen at 1000 ppm (NOAEL). This concentration was used as a starting point to derive AEGL-2 values. A total uncertainty factor of 10 was applied. The interspecies uncertainty factor was reduced to 3 based on the similarity of acute effects on the CNS produced by CNS-depressing agents in rodents and humans. Moreover, use of a default interspecies uncertainty factor of 10 would have resulted in values which are contradicted by experimental human studies in which no serious or escape-impairing effects were reported during or following 6-8 hours of exposure to 80 ppm. An intraspecies uncertainty factor of 3 was applied to account for sensitive individuals because the threshold for CNS impairment is not expected to vary much among individuals. Time scaling was performed according to the equation $C^n \times t = k$, using the default of $n = 3$ for shorter exposure periods (30 minutes and 1 hour) and $n = 1$ for longer exposure periods (8 hours), due to the lack of suitable experimental data for deriving the concentration exponent. For the 10-minute AEGL-3 the 30-minute value was used because the derivation of AEGL-3 values

was based on a long experimental exposure period and no supporting studies using short exposure periods were available for characterizing the concentration-time-response. A motion was made by John Hinz and seconded by George Rodgers to adopt the proposed AEGL-2 values for carbon disulfide for 10 minutes to 8 hours of 200, 200, 160, 100, and 50 ppm, respectively. The motion passed (YES: 16; NO: 2; Abstain:0) (Appendix H).

Regarding odor annoyance, no study was available that could be used to derive a level of distinct odor awareness (LOA). The odor of carbon disulfide depends on the purity of the compound. Purest carbon disulfide has a chloroform-like pleasant smell. However, due to decomposition products, commercially available carbon disulfide typically has an unpleasant repulsive odor of decaying radish. The quality and intensity of the odor will vary with the amount of these decomposition products that are rapidly formed by the exposure of carbon disulfide to light and air. A motion was made by Thomas Hornshaw and seconded by John Hinz that a LOA should not be derived. The motion passed unanimously (YES: 17; NO: 0; Abstain: 0) (Appendix H).

Summary of AEGL Values For Carbon Disulfide [ppm]						
Classification	10-min	30-min	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL-1 (Nondisabling)	5.0	5.0	4.0	2.5	2.0	Increase in blood acetaldehyde in humans with moderate intake of alcohol (Freundt et al. 1976b)
AEGL-2 (Disabling)	200	200	160	100	50	Inhibition of escape response in behavioral study in rats (Goldberg et al. 1964)
AEGL-3 (Lethal)	600	600	480	300	150	Lethality in rats after 4 hours (0/6 at 3000 ppm; 6/6 at 3500 ppm) (Du Pont 1966)

Formaldehyde
CAS Reg. No. 50-00-0

Chemical Manager: Mark McClanahan, CDC
Staff Scientist: Sylvia Talmage, ORNL

Sylvia Talmage reviewed the data base on formaldehyde (Attachment 13). There were approximately 22 studies with human subjects involving controlled exposures. The data base on animal studies involving acute exposures is less robust. Because formaldehyde is a carcinogen in the rat, most animal studies involved chronic exposures. The discussions for each AEGL level were long and covered ranges of topics including the threshold for sensory irritation, the range of variability in the population, and formaldehyde-induced sensory irritation in mobile homes.

Initially, AEGL-3 values of 127, 88, 70, 35, and 18 ppm for the 10-minute through 8-hour exposure durations, respectively, were proposed. The basis was no deaths in rats exposed to 350 ppm for 4

hours (Nagorny et al. 1979). Interspecies and intraspecies uncertainty factors of 3 each for a total of 10 were used. No data on time-scaling were available so the default n values of 3 and 1 were applied. It was moved by Richard Thomas and seconded by Steve Barbee to accept these values. Later, during a discussion of a proposed AEGL-2 value of 13.8 ppm across time, it was noted that the 8-hour AEGL-3 value might be too similar to the AEGL-2 value. Therefore, the original AEGL-3 values were withdrawn and new numbers were proposed. It was decided to use the two LC₅₀ values for the rat (from two different studies) to derive an n value of 3.9. The 350 ppm value was divided by a total uncertainty factor of 10 and time scaled using n = 3.9. The resulting values were 79, 60, 50, 35, and 29 ppm for the 10-minute through 8-hour exposure durations, respectively. It was moved by Richard Thomas and seconded by Steve Barbee to accept these values. The motion passed (YES: 17; NO: 1; Abstain: 0) (Appendix I).

The proposed AEGL-2 value of 8 ppm across time was discussed (as were values based on other studies), but rejected by the NAC in favor of a 30-minute exposure of human subjects to 13.8 ppm (Sim and Pattle 1957). The endpoint was nasal and eye irritation with mild lacrimation; there was adaptation to the eye irritation. It was moved by John Hinz and seconded by Richard Thomas to adopt 14 ppm (rounded up from 13.8 ppm) for all time points. The motion passed (YES: 14; NO: 2; Abstain: 2) (Appendix I). Animal cancer studies with chronic exposures to 14 ppm would be used as support. The Douglas (1974) study with exposures to 8 and 13 ppm via goggles and a mouthpiece was to be located to see if it would be relevant as a support document (only an abstract was available at the present time).

An AEGL-1 of 1 ppm for all time points, based on the weight-of-evidence from multiple studies was initially proposed. It was moved by George Rodgers and seconded by Ernie Falke to accept this value. The motion failed (YES: 8; NO: 9; Abstain: 1) (Appendix I). It was then moved by Bob Benson and seconded by Marinelle Payton to use 0.4 ppm across all time points. This value was reported as irritating in two of the many human studies. Other studies showed more severe irritation at higher exposures. The motion passed (YES: 13; NO: 3; Abstain: 1) (Appendix I).

Summary of AEGL Values for Formaldehyde						
Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL-1 ^a	0.40 ppm	0.40 ppm	0.40 ppm	0.40 ppm	0.40 ppm	Eye irritation and rhinitis - humans (Pazdrak et al. 1993; Krakowiak et al. 1998)
AEGL-2	14 ppm	14 ppm	14 ppm	14 ppm	14 ppm	Mild lacrimation with adaptation (Sim and Pattle 1957)
AEGL-3	79 ppm	60 ppm	50 ppm	35 ppm	29 ppm	Highest non-lethal value - rat (Nagorny et al. 1979)

Acetone

CAS Reg. No. 67-64-1

Chemical Manager: Mark McClanahan, CDC
Staff Scientist: Jens-Uwe Voss/Gerhard Rosner, Germany

The chemical review on acetone was presented by Jens-Uwe Voss (Attachment 14). Acetone is the most widely used ketone in industry. In 1994, worldwide production capacity was about 3.8 million tonnes. Acetone is used primarily as a solvent and to synthesize methacrylates, bisphenol A, and other ketones. Owing to its high volatility and flammability (explosive limits in air, lower: 2.6 %, upper: 12.8 % v/v), acetone poses an acute fire and explosion hazard.

In humans and other mammals, acetone is a minor metabolite of normal intermediary metabolism. Consequently, small quantities may occur in exhaled air. Endogenous acetone formation is closely linked with ketogenesis in the catabolism of body fat. Concentrations above normal levels in body tissues build up during fasting and especially in diabetic patients in the ketoacidotic state.

The primary effects in humans are irritation and effects on the central nervous system (CNS). CNS effects are also observed in animals following acute inhalation exposure. Acetone is not genotoxic *in vitro* and *in vivo*. Carcinogenicity studies are lacking, but dermal carcinogenicity studies in which acetone is used as vehicle control did not provide evidence of tumorigenic activity. Isopropanol which is primarily metabolized to acetone in mammals was not considered carcinogenic in a two-year inhalation carcinogenicity study with rats. In developmental toxicity studies with repeated exposure, reduced maternal and fetal weight was observed but the incidence of malformations was not significantly increased.

The AEGL-1 derivation is based on observations in four studies with human volunteers exposed for 3-5 minutes (Nelson et al. 1943), 2 hours (Ernstgard et al. 1999), 6 hours (Matsushita et al. 1979a) and 7.5 hours (Stewart et al. 1975). At 200 ppm, subjective symptoms (feeling of eye/throat irritation) were not reported more often than in controls (Stewart et al. 1975). At 250 ppm, no irritative symptoms on mucous membranes or effects on the CNS were observed in one study (Ernstgard et al. 1999); in a second study, slight irritation and subjective discomfort (feeling of tension, general weakness, heavy eyes, lacking in energy) was felt at 250 ppm, and these subjective symptoms were felt by most volunteers at 500 ppm and 1000 ppm (Matsushita et al. 1969a). Slight feeling of irritation at 300 ppm and subjective irritation in the majority of exposed volunteers at 500 ppm were reported in a further study (Nelson et al. 1943). Therefore, 200 ppm were selected to derive AEGL-1. Because this concentration represents a NOAEL for local effects and effects at higher concentrations were weak, an intraspecies factor of 1 was applied. The value of 200 ppm was used for all time points since accommodation to slight irritation occurs and the complaints about subjective discomfort at higher concentrations were reported not to increase during 6 hour or 7.5 hour exposure. A motion was made by Nancy Kim and seconded by Tom Hornshaw to adopt 200 ppm as AEGL-1 for all time points. The motion passed unanimously (YES: 18; NO: 0; Abstain: 0) (Appendix J).

The AEGL-2 is based on the NOAEL for ataxia in rats following exposure to 6000 ppm acetone for 4 hours (Goldberg et al. 1964). At the next higher concentration of 12,000 ppm, reversible ataxia was observed. Reversible ataxia also was observed in another study at exposure of rats to 12,600 ppm for 3 hours, but a no-effect level was not determined in that study (Bruckner and Peterson 1981a). A total uncertainty factor of 4.2 was applied. An intraspecies uncertainty factor of 4.2 was applied to account for sensitive individuals. This substance-specific factor was derived from a study with rats of different ages in which it was observed that the lethal dose of acetone via intraperitoneal injection was 4.2-fold lower in newborn than in adult rats (Kimura et al. 1971). Additionally, in humans it is consistently observed for volatile anesthetics that newborns are the most sensitive age group (NRC 2001). An interspecies factor of 1 was used: toxicokinetic studies show that following inhalation the concentration of acetone in blood is similar or lower in humans than in rats. Furthermore, with respect to toxicodynamics, effects of substances such as acetone that are non-specific acute CNS-depressants in general do not show much variation between species. Finally, an interspecies factor of 3 which is often used in the derivation of AEGLs for CNS-depressant volatile solvents like acetone would (together with an intraspecies factor of 4.2) have resulted in AEGL-2 values of 480 ppm for 4 hours and of 320 ppm for 8 hours. These values are not supported by data from controlled human studies in which higher exposures for up to 7.5 hours resulted in irritation and slight headaches but no more severe effects. Furthermore, available toxicokinetic data for humans show that an exposure to such concentrations would lead to acetone concentrations in blood below 50 mg/L. Such concentrations are still in the physiological range which can be observed in healthy fasting humans. A substance specific intraspecies uncertainty factor of 4.2 was applied to account for sensitive individuals. The experimentally derived exposure values were scaled to AEGL time frames using the equation $c^n \times t = k$ with $n = 1.7$ as outlined below for AEGL-3. A motion was made by Richard Thomas and seconded by John Hinz to adopt AEGL-2 values for acetone for 10 min., 30 min., 1 h, 4 h, and 8 h of 9300, 4900, 3200, 1400, and 950 ppm, respectively. The motion passed (YES: 15; NO: 1; Abstain: 1) (Appendix J).

The AEGL-3 is based on a study in rats in which no deaths of animals occurred at exposure to 12,600 ppm for 3 hours (Bruckner and Peterson 1981a). In that study, also no deaths were observed in animals exposed to 19,000 and 25,300 ppm, but since 1 of 6 animals died at 16,000 ppm in another study (Smyth et al. 1962), the findings at 12,600 ppm exposure for 3 hours were taken as basis for the derivation of AEGL-3. A total uncertainty factor of 4.2 was applied. An interspecies uncertainty factor of 1 was used because the same toxic effects (CNS-depression) which are relevant for AEGL-2 are also relevant in case of AEGL-3. The experimentally derived exposure values were scaled to AEGL time frames using the equation $c^n \times t = k$ with a value of $n = 1.7$ that was derived by extrapolation from 4-hour and 8-hour LC_{50} data (Pozzani et al. 1959). A motion was made by John Hinz and seconded by Tom Hornshaw to adopt AEGL-2 values for acetone for 10 min., 30 min., 1 h, 4 h, and 8 h of 16000, 8600, 5700, 2500, and 1700 ppm, respectively. The motion passed (YES: 16; NO: 2; Abstain: 0) (Appendix J).

The AEGL-2 values for 10 minutes, 30 minutes and 1 hour and the AEGL-3 values for 30 minutes, 1 hour and 4 hours are higher than 1/10 of the lower explosive limit (LEL) of acetone in air. The AEGL-3 value for 10 minutes is higher than 1/2 of the LEL of acetone in air. It was discussed and proposed to mark values higher than 1/10 of the LEL by an asterisk and to indicate in a footnote

that safety considerations against hazard of explosion must be taken into account at these levels. Similarly, it was proposed to replace values higher than 1/2 of the LEL in the table by a remark „see below“ and to present the value in a footnote together with a note that extreme safety considerations against hazard of explosion must be taken into account at these levels. Both proposals were accepted by specific count of hands for or against not recorded.

As additional information for emergency responders, a level of distinct odor awareness (LOA) was derived. The LOA is based on a median odor detection threshold of 41 ppm (Wysocki et al. 1997) and a threshold of 0.16 ppm for the reference chemical n-butanol in the same study. Wysocki et al. (1997) reported that no correlation was observed between acetone and n-butanol olfactory thresholds in that study. However, since the reference odor threshold of 0.04 ppm for n-butanol is based on a large number of data, it was discussed to use a corrected odor threshold of $41 \times (0.04/0.16)$ ppm. Using a default factor of 16, a LOA of 170 ppm was calculated. A motion was made by Richard Thomas and seconded by John Hinz to adopt a LOA of 170 ppm provided that no objection will be made by Mark Ruijten who will be asked as an expert for the calculation of odor values. The motion passed unanimously (YES:17; NO: 0; Abstain:0) (Appendix J).

SUMMARY TABLE OF AEGL VALUES FOR ACETONE [ppm] ^a						
Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL-1	200	200	200	200	200	NOAEL for slight irritation (Ernstgard et al. 1999; Matsushita et al., 1969a; Nelson et al. 1943; Stewart et al. 1975)
AEGL-2	9,300*	4,900*	3,200*	1,400	950	Ataxia in rats (Bruckner and Petersen 1981a; Goldberg et al. 1964)
AEGL-3	see below #	8,600*	5,700*	2500*	1,700	No lethality in rats (Bruckner and Petersen 1981a; Smyth et al. 1962)

a: Cutaneous absorption of liquid acetone may occur. Since liquid acetone is an eye irritant, eye contact must be avoided.

#: The AEGL-3 value of 16,000 ppm (39,000 mg/m³) for 10 minutes is higher than 50 % of the lower explosive limit of acetone in air (2.6 % = 26,000 ppm). Therefore, extreme safety considerations against the hazard of explosion must be taken into account.

*: Concentrations are higher than 1/10 of the lower explosive limit of acetone in air (2.6 % = 26,000 ppm). Therefore, safety considerations against the hazard of explosion must be taken into account.

Level of distinct odor awareness: 170 ppm (Odor detection threshold in humans; Wysocki et al. 1997).

Vinyl Chloride CAS Reg. NO. 75-01-4

Chemical Manager: Bob Benson, EPA
Staff Scientist: Fritz Kalberlah, Germany

Susan Ripple, liaison for the American Chemistry Council to the NAC/AEGL fulfilled the request to provide insight on the issue of whether headaches in a few individuals can be attributed to vinyl chloride exposure (Attachment 15). Susan Ripple pointed out that there are 3 studies: Lester et al. 1963, Baretta et al. 1969, and further supported by Patty et al. 1930. These three studies found that at least some individuals developed headaches that lasted only 30 minutes at higher exposure-levels. This is consistent with anecdotal information from industry assessments. A detailed explanation of the carcinogenicity issue was presented, providing numbers of exposed workers in the cohort studies by Ward et al. 2000 and Mundt et al. 1999. Overall, there were 12,700 subjects in the vinyl chloride cohort study by Ward, with an SMR of 62 in 10,961 workers of less than 3 years exposure that developed liver cancer (ASL). Another way to look at these values is to calculate the ppm.years, where the ASL incidence in the unknown exposure population was 67, and for 1-734 ppm.years was an SMR of 107. Mundt likewise was presented in terms of length of exposure, with an SMR of 83 incidence of ASLs in the 1-4-year exposure time frame. The discussion of higher sensitivity in young and newborn rats as a possible cancer risk assessment approach was presented as highly uncertain as the studies by Maltoni et al. 1981 had study-design and reporting flaws.

Chemical Manager, Bob Benson, responded to Susan Ripple's comments on the derivation of AEGL-1, AEGL-2, and the cancer assessment. For AEGL-2 Susan Ripple suggested that the NAC consider using a higher exposure (16,000 ppm for 5 minutes) from Lester et al. (1963) as the starting point for the derivation. Bob Benson later indicated that the effects observed at this exposure (dizziness, light headedness, some nausea, and dulling of visual and auditory cues) were beyond the "threshold" for effects meeting the definition of AEGL-2. The NAC/AEGL used the next lower exposure of 12,000 ppm exposure as the equivalent of the "threshold" for effects that would impair the ability to escape and there was no need to reconsider this decision. For AEGL-1 Susan Ripple suggested that the NAC/AEGL consider using the same study and exposure as originally used (Baretta et al., 1969) but use 7 hours as the exposure duration. The justification was based on the fact that the original study did not make clear whether the headache occurred during the first 3.5 hours or the subsequent 3.5 hours of exposure. Bob Benson later responded and agreed that the wording in the publication did not make it absolutely clear when the headaches occurred but a reasonable interpretation of the text was that headache occurred in some individuals during both exposures. The wording in the text is "The only complaints were those of two subjects who reported mild headache and some dryness of their eyes and nose during the 500 ppm exposure experiments." A logical interpretation is that the authors consider there were two experiments - one with an exposure duration of 3.5 hours, and the other with an exposure duration of 7.5 hours (3.5 hours, a break of 0.5 hours, and then additional exposure of 3.5 hours) - and that headache was noted by two individuals during both exposures. Therefore it was logical to use 3.5 hours as the time required for headache as the NAC/AEGL had previously done. Therefore, there was no need to reconsider this decision. Susan Ripple also presented a discussion of another epidemiological study of workers exposed to vinyl chloride and occurrence of cancer (Ward et al., 2000). There appeared to be no increase in cancer following short term exposure. However, it was not clear whether actual exposure to VC was known. Susan Ripple agreed to provide a brief summary of this information for inclusion in the Technical Support Document.

Fritz Kalberlah presented a discussion of the cancer assessment (Attachment 16). The appendix included a cancer calculation for continuous lifetime exposure using the default procedure in the

SOP; a cancer calculation based on childhood exposure using the unit risk estimate for childhood exposure derived by EPA; a cancer calculation based on derivation of a unit risk estimate from a five-week animal study from Maltoni et al. (1981); and a calculation based on the occurrence of DNA adducts after a single in vivo exposure of adult animals. There was considerable discussion about these calculations and how best to draw attention to the calculations in the Executive Summary of the Technical Support Document. Bob Benson and Fritz Kalberlah agreed to consider various alternatives and present these at a future NAC/AEGL meeting. The NAC/AEGL also requested that information on transplacental carcinogenicity be added to the document.

Hydrogen Bromide
CAS Reg. No. 10035-10-6

Chemical Manager: Larry Gephart
Staff Scientist: Sylvia Talmage, ORNL

Sylvia Talmage reviewed the sparse data base for hydrogen bromide (Attachment 17). The AEGL-1 was based on the only available clinical study in which subjects were exposed to concentrations between 2 and 6 ppm for short periods of time (Conn. Dept. of Health 1955). 3 ppm was the NOAEL for notable discomfort as evidenced by nose and throat irritation (assumed to be slight) in 1 of 6 subjects. The 3 ppm value was divided by an intraspecies uncertainty factor of 3. No time scaling was applied because adaptation occurs to the slight irritation that defines the AEGL-1. It was moved by John Hinz and seconded by Nancy Kim to accept the AEGL-1 value. The motion passed (YES: 16; NO: 0; Abstain: 0) (Appendix K).

In the absence of chemical-specific data, it was proposed that the HBr AEGL-2 values be based on a structure-activity relationship with other hydrogen halides. The proposal to base the HBr AEGL-2 on hydrogen fluoride (HF) was rejected in favor of basing the values on the more chemically similar hydrogen chloride (HCl). It was moved by Mark McClanahan and seconded by Nancy Kim to accept the HCl values for the 10-minute to 8-hour time periods of 100, 43, 22, 11, and 11. The motion passed (YES: 15; NO: 0; ABSTAIN: 0) (Appendix K).

In response to earlier Committee suggestions, the benchmark concentration approach was used to develop AEGL-3 values. One-hour rat lethality data generated by MacEwen and Vernot (1972) were used. The BMCL₀₁ was suggested, but this suggestion was rejected in favor of the BMCL₀₅ (the BMCL₀₅ is the suggested approach in the SOPs). After much discussion it was moved by Ernie Falke and seconded by John Hinz to accept the BMCL₀₅ values of 740, 250, 120, 31, and 31 ppm. The 4-hour and 8-hour values were set equal as was done for HCl and HF, because all of these hydrogen halides are well scrubbed at lower concentrations. The motion passed (YES: 16; NO: 0; ABSTAIN: 0) (Appendix K).

SUMMARY OF AEGL VALUES FOR HYDROGEN BROMIDE (ppm)						
Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint
AEGL-1	1	1	1	1	1	NOAEL for notable discomfort - humans
AEGL-2	100	43	22	11	11	Analogy with hydrogen chloride
AEGL-3	740	250	120	31	31	Benchmark concentration - rat lethality data

Boron Trifluoride
CAS Reg. No. 353-42-4

Chemical Manager: George Rusch, Honeywell
Staff Scientist: Claudia Troxel, ORNL

Experimental data will be available in later part of the year; then the TSD will be revisited accordingly.

Titanium tetrachloride
CAS Reg. No. 7550-45-0

Chemical Manager: Tom Hornshaw, Illinois EPA
Staff Scientist: Claudia Troxel, ORNL

The chemical review was presented by Claudia Troxel (Attachment 18). The AEGL-3 values were based on one-third of the rat LC₅₀ values reported by Kelly (1980). The adjusted, empirical values (1/3 of the values) for the 30, 60, and 240-minute exposure durations were used for the respective AEGL time points. Using an n=0.88, the adjusted, 15-minute LC₅₀ value was used to extrapolate to 10 minutes, while the adjusted 240-minute LC₅₀ value was used to extrapolate to 480 minutes. A total uncertainty factor of 10 was applied to be consistent with available toxicity data. A motion was made by Loren Koller and seconded by Richard Thomas to adopt the proposed AEGL-3 values. The motion passed unanimously (YES: 17; NO: 0; Abstain: 0) (Appendix L).

The AEGL-2 was based on the exposure concentration of 1.3 ppm titanium tetrachloride for 6 hours/day, 5 days/week for 4 weeks (Kelly, 1979). Although no clinical signs were observed at this concentration, using the next higher exposure concentration of 6.5 ppm for 6 hours/day, 5 days/week for 4 weeks (Kelly, 1979) results in values approaching the lethality threshold. A total uncertainty factor of 10 was applied to be consistent with available toxicity data. The value was then scaled across time using the derived value of n=0.88. The 10-minute value was initially set equal to the 30-minute value because the NAC considers it inappropriate to extrapolate from an exposure duration of 6 hours to 10 minutes. A motion was made by Loren Koller and seconded by Richard Thomas to adopt the proposed AEGL-2 values. However, it was brought out at the end of

the meeting that the AEGL-2 starting value could be scaled to the 10-minute time-period because the derived value of n used time points encompassing that particular time point. Therefore, the motion was amended so that the 10-minute AEGL-2 value would now be 7.6 ppm (instead of 2.2 ppm) following scaling across time. The motion passed (YES:17; NO: 0; Abstain: 0) (Appendix L).

No acute toxicity data relevant to the definition of an AEGL-1 endpoint are available. Therefore, the 0.7 ppm exposure for 6 hours/day was used to provide a general baseline of an exposure concentration at which no one should experience notable discomfort, irritation, or certain asymptomatic, non-sensory effects. A total uncertainty factor of 10 was applied (3 for interspecies and 3 for intraspecies) because the endpoint selected is below the endpoint defined for the AEGL-1 tier and because the study was a multiple exposure study. The value, 0.070 ppm, was then set equal across time. A motion was made by Loren Koller and seconded by Richard Thomas to adopt the proposed AEGL-1 values. The motion passed (YES:16; NO: 0; Abstain:0) (Appendix L).

Because titanium tetrachloride forms an aerosol upon contact with moist air, the AEGL values should be presented only in terms of mg/m³, as was done for the chemical boron trifluoride.

Summary of Proposed AEGL Values for Name of Titanium Tetrachloride [mg/m ³]						
Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL-1 (Nondisabling)	0.54	0.54	0.54	0.54	0.54	No clinical signs observed in rats exposed to 0.7 ppm for 6 h/d, 5 d/wk for 4 wks (Kelly, 1979)
AEGL-2 (Disabling)	59	17	7.8	1.6	0.73	Exposure of rats to 1.3 ppm for 6 h/d, 5 d/wk for 4 wks resulted in no clinical signs, but next exposure level approaches lethality threshold (Kelly, 1979)
AEGL-3 (Lethal)	290	100	44	16	7.1	One-third the rat LC ₅₀ values (Kelly, 1980)

Administrative Matters

The site and time of the next meeting, NAC/AEGL-29, was decided to be June 17-19, 2003 in Washington, D.C. The date for NAC/AEGL-30 has been set tentatively as September 16-18, 2003 in Washington, D.C. The NAC/AEGL-31 has two options (1) early December in San Antonio or (2) Dec. 15-17, 2003 in Washington, D. C. More information regarding the NAC/AEGL-29 hotel information will be coming from Po-Yung Lu as soon as the arrangement is made.

All items in the agenda were discussed as thoroughly as the time permitted. The meeting highlights were prepared by Po-Yung Lu and Sylvia Talmage, Oak Ridge National Laboratory, with input from the respective Chemical Managers, authors, and other contributors.

LIST OF ATTACHMENTS

The attachments were distributed during the meeting and will be filed in the EPA Docket Office.

- Attachment 1. Status update from EPA on Human Subject Studies
- Attachment 2. Excerpt from SOP on selection of Human Studies for TSD Preparation
- Attachment 3. NAC/AEGL-27 Meeting Agenda
- Attachment 4. NAC/AEGL-27 Attendee List
- Attachment 5. Status Report of Category V chemicals: Critical Health Effect Starting Points for AEGL Determination: LOAEL vs. NOAEL
- Attachment 6. Basic Occupational Exposure Assessment
- Attachment 7. Proposal of Information Be Included in Exposure Assessment of TSDs
- Attachment 8. Application of Acute Exposure Guideline Levels
- Attachment 9. Data Analysis of Iron pentacarbonyl
- Attachment 10. Data Analysis of Ethyleneimine and Propyleneimine
- Attachment 11. Data Analysis of Piperidine
- Attachment 12. Data Analysis of Carbon Disulfide
- Attachment 13. Data Analysis of Formaldehyde
- Attachment 14. Data Analysis of Acetone
- Attachment 15. Data Analysis of Vinyl Chloride, ACC, Susan Ripple
- Attachment 16. Data Analysis of Vinyl Chloride, Fritz Kalberlah
- Attachment 17. Data Analysis of Hydrogen Bromide
- Attachment 18. Data Analysis of Titanium Tetrachloride

LIST OF APPENDICES

- Appendix A. Revised meeting highlights of NAC/AEGL-26 (sent to NAC/AEGL on 3/28/2003 by E-mail).
- Appendix B. Ballot for Acceptance of the Status Report of NOAEL vs LOAEL (March 3, 2003)
- Appendix C. Ballot for Acceptance of Occupational Exposure Measurement Information (proposals: 1 and 2).
- Appendix D. Ballot for Iron Pentacarbonyl
- Appendix E. Ballot for Iron Pentacarbonyl
- Appendix F. Ballot for Ethyleneimine
- Appendix G. Ballot for Piperidine
- Appendix H. Ballot for Carbon Disulfide
- Appendix I. Ballot for Formaldehyde
- Appendix J. Ballot for Acetone
- Appendix K. Ballot for Hydrogen Bromide
- Appendix L. Ballot for Titanium Tetrachloride

Attachment 1

The NAC/AEGL is working to ensure that emergency responders in this country and abroad are armed with the vital information they need to protect the public and themselves from harm in the event of chemical accidents or homeland security emergencies. This program uses domestic and international existing test data, both animal and human, to determine levels of harm for a range of exposure scenarios critical to those at the front line in defending public health. The NAC/AEGL is also committed to the appropriate use of human study information in developing AEGL values to ensure health protective emergency response actions.

For this reason, EPA is asking that the NAC/AEGL adopt an explicit step early in the AEGL value development process to make a determination that all human studies to be considered have been conducted in accordance with the program's Standard Operating Procedures and were ethically conducted. If there are any studies that do not meet this criteria, they would be rejected from further consideration in the development of the values for that chemical.

The NAC/AEGL Committee is dependent upon existing clinical, epidemiologic, and case report studies published in the literature for data on humans. Many of these studies do not necessarily follow current guidelines on ethical standards that require effective, documented, informed consent from participating humans subjects. Further, recent studies that followed such guidelines may not include that fact in the publication. Although human data may be important in deriving AEGL values that protect the general public, utmost care must be exercised to ensure first of all that such data have been developed in accordance with ethical standards. No data on humans known to be obtained through force, coercion, misrepresentation, or any other such means will be used in the development of AEGLs. The NAC/AEGL Committee will use its best judgment to determine whether the human studies were ethically conducted and whether the human subjects were likely to have provided their informed consent. Additionally, human data from epidemiologic studies and chemical accidents may be used. However, in all instances described here, only human data, documents, and records will be used from sources that are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified directly or indirectly. These restrictions on the use of human data are consistent with the "Common Rule" published in the *Code of Federal Regulations* (Protection of Human Subjects, 40 CFR 26, 2000).

National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances

NAC/AEGL-28
March 7-8, 2003

Eagle Gate East & West
Best Western Salt Lake Plaza Hotel
122 West South Temple
Salt Lake City, Utah 84101
801-521-0130

AGENDA

Friday, March 7, 2003

8:00 a.m.	Introductory remarks and approval of NAC/AEGL-27 Highlights (George Rusch, Roger Garrett, and Paul Tobin)
8:15	Highlights of COT/AEGL January meeting (Ernie Falke and George Rusch)
8:30	Report on LOA data quality (Mark McClanahan and Marc Ruijten)
9:00	Resolution of LOAEL vs NOAEL on Iron pentacarbonyl (Ernie Falke)
9:30	Overview of fundamental principles of industrial hygiene (John Morawetz)
10:00	Break
10:15	AEGL application: Relevance to occupational exposure (George Rusch)
10:30	Review of Carbon disulfide: AEGL-2 (George Rodgers/Jens-Uwe Voss)
11:45	Lunch
1:00 p.m.	Review of Formaldehyde (Mark McClanahan/Sylvia Talmage)
3:00	Break
3:15	Review of Acetone (Mark McClanahan/Jens-Uwe Voss)
5:15	Adjourn for the day

Saturday, March 8, 2003

8:00 a.m.	Review of Vinyl chloride: <ul style="list-style-type: none">❖ Q1*derivation (Susan Ripple, ACC)❖ Carcinogenicity assessment (Bob Benson/Fritz Kalberlah)
9:45	Break
10:00	Report on LOA values of Ethylenimine and Propylenimine (Mark McClanahan/Kowetha Davidson)
10:30	Review of Hydrogen bromide (Larry Gephart/Sylvia Talmage)
11:45	Status report of Boron trifluoride testing (George Rusch)
12:00 noon	Lunch
1:00	Review of Piperidine (Mark McClanahan/Kowetha Davidson)
2:00	Break
2:15	Review of Nitric acid (Loren Koller/Carol Wood)
3:15	Review of Titanium tetrachloride (Tom Hornshaw/Claudia Troxel)
5:00	Administrative matters
5:15	Adjourn meeting

NAC/AEGL-28

Attachment 4

March 7-8, 2003

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March 3, 2003

TO: Roger Garrett and George Alexeeff

FROM: Po-Yung Lu

SUBJECT: Status Report of NOAEL/LOAEL Consistency Concerns for AEGL Development

CC: Ernie Falke, George Rusch, Paul Tobin

This status report provides a summary on the subject of critical health effect starting points for AEGL determination: "NOAEL/LOAEL Consistency Concerns for AEGL Development". This report captures the highlights of several discussions that took place at the NAC/AEGL meetings, and subsequent correspondence. As indicated in this report, you will find that most of the TSDs identified in George Alexeeff's memo of August 1, 2002 were clarified just in time and moved forward to NAC/AEGL review or COT/AEGL review and publication. In the case of only a few of the TSDs (HCFC 141b, Otto Fuel, and Phosgene) published in 2002, ORNL was not able to make any changes in time since they were approved by COT/AEGL for publication and final TSDs were sent to NAS in April 2002. However, for these three chemicals, any necessary modifications to the TSDs will be made when AEGL values might be revisited in the future.

Background Information:

George Alexeeff submitted a letter (February 6, 2002, distributed at the NAC/AEGL-25 meeting) with a list of 33 chemicals for which he was concerned that the NAC/AEGL Committee is not consistently following the Standing Operations Procedures Manual (2001), as described on pages 36, 40, and 42. The chemicals presented in the letter are examples of his concern that the NAC/AEGL Committee did not identify a NOAEL, but rather used a LOAEL as the starting point for AEGL development, without an additional safety (UF/MF) factor correction to obtain a "NOAEL". Subsequently, the EPA AEGL Program (Roger Garrett and Letty Tahan), with ORNL staff input, conducted an analysis and subdivided the 33 chemicals in question into the following five categories below for ease of discussion (also distributed at the NAC/AEGL-25 meeting). They are:

- Category I: Observed effect level is < the AEGL threshold level
- Category II: Observed effect is adjusted from a LOAEL to a NOAEL using a UF, or a MF, or an adjustment factor, e.g. $LC_{50}/3$.
- Category III: Observed effect level is adjusted from a LOAEL to a NOAEL based on circumstances surrounding the study in question, e.g., multiple exposures.
- Category IV: Revisions expected based on NAS/COT-AEGL Subcommittee review.
- Category V: Observed effect > the AEGL threshold level.

After George and Roger's presentations and discussion at NAC/AEGL-25 (June 17-19, 2002), it was agreed that only Category V chemicals need further clarification and justification. George Alexeeff further prepared a response (dated August 1, 2002) to the AEGL Programs's analysis. Roger requested that the TSD Development Team prepare the responses to address these concerns, particularly the Category V chemicals. The responses to Category V chemicals were distributed prior the NAC/AEGL-27

(Dec. 9-11, 2002) meeting and were discussed and accepted by NAC/AEGL in Dec. 2002. However, George Alexeeff had a continuing concern about iron pentacarbonyl. Although this chemical had been reviewed and approved in the NAC/AEGL-25 meeting (June 2002) and is close to approval by COT/AEGL, it will be revisited at the upcoming NAC/AEGL-28 meeting in March 7-8, 2003 in Salt Lake City, Utah.

Response Status Report to August 1, 2002 Memo:

Category 1 Chemicals:

*** Chlorine:**

The staff interpretation is correct. The TSD has been revised accordingly and submitted to NAS, COT/AEGL for review in January 2003.

*** Chlorine trifluoride:**

As stated in the AEGL Program staff response, nasal discharge from the sensitive nose of the dogs is a NOAEL for the AEGL-1. This is explained in the revised TSD and was approved in NAC/AEGL-27.

*** Crotonaldehyde:**

Mild eye irritation is not considered notable discomfort; it is clarified in the revised TSD which was recently reviewed by COT/AEGL in January 2003.

*** Diborane:**

Inflammatory epithelial degeneration in the bronchioles in male ICR mice is a reversible histological change. The TSD was modified to reflect that this change is not a LOAEL. The Diborane TSD has been accepted by COT/AEGL for final publication.

*** 1,2-Dichloroethylene:**

The TSD is on a holding status for modeling work; however, corrections will be made during the revision.

*** Ethylene oxide:**

Clarification will be made in the next revision. Afterwards, the TSD will be ready for COT/AEGL review in July 2003.

*** Ethylenediamine:**

Clarification has been made to reflect the comment. The revised TSD was reviewed in January 2003 by COT/AEGL. Approval for publication is expected in the next (9th) Interim Report.

*** Hydrazine:**

Clarification will be made to fit the AEGL-2 definition of a NOAEL. The revised TSD will then be ready for COT/AEGL final review for publication in July 2003.

*** Hydrogen fluoride:**

The TSD was revised accordingly. The TSD was reviewed at the January 2003 COT/AEGL meeting. Approval for final publication is expected in the 9th Interim Report.

*** Otto Fuel:**

Final TSD was submitted to NAS in April and published by NAS in Volume 2, 2002.

*** Phosgene:**

Final TSD was submitted to NAS in April and published by NAS in Volume 2, 2002.

*** Sulfur Mustard:**

There was a typographical error in the staff response report of June 2002. The statement "not reversible" should have been "not irreversible." No correction was needed as the proper statement was already contained in the TSD. In addition, the effect had already been termed a threshold which meets the definition of each AEGL level. This TSD is considered final and has been approved for publication by NAS.

* Tetrachloroethylene:

This chemical is on hold until PBPK modeling can be performed. The staff response is that mild eye irritation is a NOAEL for the AEGL-1; this will be clarified in the next revision and moved forward to COT/AEGL review.

* Toluene:

Following rejection by the COT/AEGL, the TSD was totally rewritten. This revised version was approved by the NAC/AEGL-27.

Category II Chemicals:

* Hydrogen chloride:

Clarification was made and the revised TSD was reviewed by COT/AEGL in January 2003. Approval for publication is expected in the 9th Interim Report.

Category III Chemicals:

* Carbon monoxide:

The staff response states that the reduced time to onset of angina during physical exercise of coronary disease patients was a reversible effect that is not considered an impairment to escape. This will be clarified in the revision when recycled to a future COT/AEGL meeting.

* HCFC 141b:

Final TSD was submitted to NAS in April and published by NAS in Volume 2, 2002.

* Sulfur Mustard:

The TSD was revised accordingly and is at NAS for final publication.

Category IV Chemicals:

No specific chemicals were identified since the endpoints are undergoing revision in response to COT/AEGL comments.

Category V Chemicals:

There were six chemicals identified in the EPA AEGL Program analysis report prepared by Roger Garrett and Letty Tahan with input from ORNL staff members in June 2002. Specific responses were prepared and distributed prior the NAC/AEGL-27 meeting. The responses were reviewed and accepted by NAC/AEGL during the meeting except for a concern by George Alexeeff on Iron pentacarbonyl. This chemical will be revisited at the NAC/AEGL-28 meeting.

This is a complete status report on the subject of critical health effect starting points for AEGL determination: "NOAEL/LOAEL Consistency Concerns for AEGL Development". If there are any questions, please let me know.

Basic Occupational Exposure Assessment

John S. Morawetz

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Center for Worker Health & Safety Training

Cincinnati, Ohio

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Exposure Assessment

- Variability of exposure in an occupational environment vs. chamber study
- Types of occupational samples
- Time to collect sample

Chamber Studies

- Goal: Constant exposure level
- Same exposure concentration
 - Over time
 - Over location

Occupational Exposures

- Highly variable exposure
- Primarily driven by work processes and job tasks
- Different levels at various locations
- Workers move around the workplace

Types of Samples

- Bulk
 - Processing equipment, storage containers
- Area
 - Occupational vs. Environmental
 - Useful for control technology
- Personal: Breathing Zone

Time to collect sample

- Instantaneous/Grab samples
- Time Weighted Average
 - Commonly 8 hour sample
 - Can range from 15 minutes to 8 hours
 - Short term: usually 15 minutes
- Time to collect exposure sample may not equal time of worker's exposure

The AEGL Standard Operating Procedures (SOP) includes a section on Evaluation, Selection, and Documentation of Key and Supporting Data (Section 2.3.2). This section covers the description and how exposures are determined:

5) Scientifically credible exposure concentration and exposure duration for the study are provided.

In using occupational studies, exposures and their measurement are not the same as in animal or human chamber studies. In chamber cases, exposures are generally controlled and often uniform both over time, within the chamber and therefore for all subjects. In occupational exposures, this is not the case. Exposures vary significantly over time, by area and by person. The variability of personal samples within the same department is estimated to range from 10 to 4,000 fold. Area samples can significantly underestimate or overestimate personal exposures depending on the location of the area samples in relation to the source of contamination and where workers perform their jobs for specific time periods. Estimates of the variability between area and personal samples can be up to 100 fold while other authors have found there is no correlation. Additionally, there is no assurance that workers in various departments in the same facility will have the same exposures unless specific evidence in the form of individual sampling data is presented. In animal and chamber studies, exposure measurements are often performed continuously or at regular intervals to assure that exposure is well controlled and constant. In occupational studies with more variability, there often is less data.

In occupational studies there are two time durations: first the duration that the sample was taken and second, the duration that the worker was exposed. It's critical in the description of occupational studies that both time elements are reported, namely the duration of workers' exposures and the duration of the exposure measurement. In addition, if an exposure measurement is not a personal sample (area, bulk or calculated), this must be clearly noted. These are basic fundamentals of industrial hygiene which are noted in the references below.

The AEGL committee should amend the SOP's elements for Key and Supporting Documents in the following areas to accurately describe and use occupational exposure measurements:

Bulk samples

1a) Bulk samples and theoretical calculations from bulk samples are not measurements of workers' exposures. Bulk sample and theoretical calculation levels should be clearly described as such.

1b) Bulk samples and theoretical calculations from bulk samples should generally not be utilized in the AEGL derivation sections unless there is substantial documentation on workers' tasks and their relationship to these samples.

Area samples

2a) Area samples are not a measurement of workers' exposures. Area or general workplace air levels should be clearly described as such.

2b) Area or general workplace air levels should generally not be utilized in the AEGL derivation sections unless there is substantial documentation on workers' tasks and their relationship to these samples.

Short term samples

3a) Short term samples are not a measurement of workers' full shift exposure. All short term samples should be clearly described as such.

3b) Short term levels should generally not be utilized in the AEGL derivation sections unless there is clear evidence that they were personal samples and then only with the appropriate measurement time.

Multiple workplace studies

4) When studies investigate multiple workplaces, exposure assessments from one of these worksites can not be extrapolated to the conclusion of the entire study. Descriptions of the exposure levels found in these studies should clearly state the specific number of worksites to which these exposure levels pertain.

To incorporate these points in the SOP, the following language should be added to the SOP's Evaluation section.

In using occupational studies,

1) Breathing zone samples are the preferred estimate of workers' exposures. All breathing zone samples should be described as such.

2) Area, general workplace, bulk samples and theoretical calculations from bulk samples should be clearly described as such.

3) Usually general workplace, bulk samples and theoretical calculations from bulk samples are not necessarily accurate measurements of workers' exposures. They should not be utilized in the AEGL derivation sections unless there is substantial documentation on workers tasks and the relationship to these samples.

4) Breathing zone short term samples should be described as such and used primarily for the sampled time period.

5) Exposure assessments from a single workplace in a multiple workplace study usually can not extrapolate to exposures for other workplaces in the study. Descriptions of the exposure levels found in these studies should clearly state the number of worksites that found any specific exposure levels. This should also include the number, duration and types of measurements.

References

Fundamentals of Industrial Hygiene, J. Olishifski Editor, Second Edition, 1979

Chapter 15: Industrial Toxicology; R. Smith, J. Olishifski

Chapter 16: Evaluation; E. Hermann, J. Peterson

Chapter 17: Methods of Evaluation; J. Olishifski

Chapter 18: Air Sampling Instruments; J. Olishifski

Chapter 19: Direct Reading Gas and Vapor Monitors; J. Zatek

The Industrial Environment – its Evaluation and Control; NIOSH, 1973

Chapter 8: Principles and Use of Standards of Quality for the Work Environment; B. Dinman

Chapter 10: General Principles in Evaluating the Occupational Environment; A. Hosey

Chapter 50: An Industrial Hygiene Survey Checklist; R. Soule

Mulhausen, J. Damiano J. (1998): *A Strategy for Assessing and Managing Occupational Exposures*. 2nd Edition, American Industrial Hygiene Association, Fairfax, Virginia, pages 104-105.

Patty's Industrial Hygiene and Toxicology; Volume III: Theory and Rationale of Industrial Hygiene Practice; L. Cralley, 1979

Chapter 6: Measurement of Worker Exposure; J. Lynch

Patty's Industrial Hygiene; Volume 1; 2000; R. Harris

Chapter 18; Interpreting Levels of Exposures to Chemical Agents; Rappaport, S.

Occupational Exposure Sampling Strategy Manual, N. Leidel et. al.; NIOSH, 1977

Technical Appendix C, The Inadequacy of General Air (Area) Monitoring for Measuring Employee Exposures

Application of Acute Exposure Guideline Levels

The Acute Exposure Level Guidelines have been developed primarily to provide guidance in situations where there can be a rare, typically accidental exposure to a particular chemical that can involve the general public. They, therefore, differ from PELs, TLV®s, WEEL®s, RELs or MAK values etc. in that they are based primarily on acute toxicology data and not subchronic or chronic data. The guidance therefore does not reflect the effects that could result from frequent exposure. Also, they are designed to protect the general population including the elderly and children, groups that are generally not considered in the development of workplace exposure levels. Users of the AEGL TSDs should first determine if there are legally enforceable standards that apply to the situation. Other organizations may also have recommended levels of exposure that more appropriately apply to the scenarios under evaluation.

It is however recognized that there may be an occasion where it may seem desirable to use these values for other exposure scenarios. In these cases, one should consult the technical support document. This document contains a comprehensive review of all identified acute toxicology data on the subject chemical and the basis for the development of the AEGL values. From this review one will have the information to determine the applicability of the AEGL to their particular situation.

**ETHYLENIMINE
AND
PROPYLENIMINE**

**LEVEL OF ANNOYANCE
ANALYSIS**

**NAC/AEGL MEETING
MARCH 7-8, 2003
SALT LAKE CITY, UT**

PROPYLENIMINE

Data are not available for an LOA analysis

ETHYLENIMINE

Population distribution of perceived odor intensity under field conditions.

Determine values for parameters

Intensity	I	3.00	Typically use 3 (distinct) or 4 (strong)
Weber-Fechner coefficient	Kw	2.33	Defaults to 2.33
GSD dor odor threshold		4.00	Defaults to 4.0
Lab-to-field adjustment		4.00	Defaults to 4.0
Peak-to-mean concentration		0.33	Defaults to 0.33
Standard normal deviate		1.2816	Use 1.2816 for 10 / 90 % response estimates Use 1.645 for 5 / 95 % response estimates

Odor threshold in ppm	OT50	OT low	OT high	LOA
<i>Ethylene imine</i>	0.6980	0.1362	3.5782	10.8991
				26.2800

Odor intensity for extremes of population at LOA concentration

Odor intensity for most sensitive subgroup	4.93	on intensity scale 0-6
Odor intensity for least sensitive subgroup	1.63	on intensity scale 0-6

Concentration required to produce LOA condition in extremes of population

LOA concentration for most sensitive subgroup	2.1261	ppm
LOA concentration for least sensitive subgroup	55.8732	ppm

IRON PENTACARBONYL - ALTERNATIVE DERIVATION OF AEGL-3 FROM BENCHMARK DOSE CALCULATION

1. ORIGINAL CALCULATION OF AEGL-3

The point of departure (POD) used for the derivation of iron pentacarbonyl AEGL-3 levels was based upon a BASF, 1995 study in which rats were exposed for up to 28 days to 0.1, 0.3, 1, 2.91, and 9.85 ppm. After 1 exposure 10/10 rats died at 10 ppm and 1 of 10 died after a single exposure to the 2.91 ppm level. Five out of 10 rats died after two exposures within 4 days. What is noteworthy is that no clinical signs were observed in rats given 28 exposures of 0.1 to 1 ppm, although some rats in the 1.0 ppm group were found (upon necropsy) to have increased absolute and relative lung weights. This data set alone demonstrates that iron pentacarbonyl has an extremely steep dose-response curve going from almost no effects to 100% mortality within a factor of 10.

The text from the original TSD follows in italics:

7.3 *Derivation of AEGL-3*

Because of the availability of analytically determined exposure concentrations and overall study quality, data from the BASF (1995) study has been used to derive AEGL-3 values. In this study, a single 6-hour exposure to 2.91 ppm resulted in the death of one of 10 rats while a second exposure produced 50% mortality. The remaining five rats survived an additional 26 6-hour exposures. The 6-hour exposure to 2.91 ppm is used as the determinant for the AEGL-3 values and its use as an estimated lethality threshold is supported by the estimated 4-hour lethality threshold of 5.2 ppm (Biodynamics, 1988), and the estimated 4-hr LC₅₀ of 10 ppm and 4-hr LC₁₆ of 6.99 ppm provided by the Biodynamics (1988) report. The resulting AEGL-3 values are supported by the slightly greater values derived using the Gage (1970) data.

The available data in rats and mice suggest that the exposure response curve for iron pentacarbonyl is steep. Exposure-response data for the same toxicity endpoint over multiple time periods is limited (30-minute LC₅₀ and 4-hr LC₅₀) for iron pentacarbonyl. Data are unavailable for a definitive mathematical determination of the time scaling factor, n, for the equation $C^n \times t = k$ (Appendix C). However, the available lethality data appear to indicate that a near-linear relationship exists. For example, the cumulative exposures for the 30-minute LC₅₀ of 118 ppm (Sunderman et al., 1959) and the 4-hour LC₅₀ of 10 ppm (Biodynamics, 1988) are 59 and 40 ppm hrs, respectively. Furthermore, if one were to scale the 30-minute LC₅₀ of 118 ppm to 4 hours, the use of n = 1 results in a 4-hour predicted value of 14.75 ppm which is consistent with the reported 4-hour LC₅₀ of 10 ppm.

In the absence of human data, and some variability among the laboratory species tested, uncertainty exists regarding species variability. Therefore, an uncertainty factor of 10 is applied to account for interspecies variability in the toxic response to iron pentacarbonyl. The

uncertainty adjustment for intraspecies variability was limited to a UF of 3 for several reasons. The available toxicity data indicate that acute inhalation exposure to iron pentacarbonyl results in port-of entry effects (i.e., airway and lungs) rather than systemic effects and, therefore, variability in response due to dosimetric factors may be limited. Additionally, lethality in rats following acute inhalation exposure to iron pentacarbonyl exhibits a steep exposure-response relationship with little margin between minimal and lethal effects, and little individual variability in the response of test animals (Biodynamics, 1998). Adjustment of the AEGL-3 values by application of greater uncertainty was not considered necessary because the total uncertainty factor of 30 resulted in AEGL-3 values that were reasonable when compared to the acute exposure data and to the data from multiple-exposure animal studies. The draft AEGL-3 values for iron pentacarbonyl are shown in Table 9 and their derivation is presented in Appendix A.

TABLE 9. AEGL-3 Values for Iron Pentacarbonyl					
AEGL Level	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-3 (Lethal)	3.5 ppm	1.2 ppm	0.58 ppm	0.15 ppm	0.073 ppm

Under ambient atmospheric conditions; iron pentacarbonyl may undergo photochemical decomposition to iron nonacarbonyl and carbon monoxide, or burn to ferric oxide.

2. COMMENTS RECEIVED AS A RESULT OF THE LOAEL-NOAEL ANALYSIS

Concern was raised in the December 2002 NAC/AEGL meeting that we had used an effect level for the Point of Departure (1 of 10 animals exposed to 2.91 ppm for 6 hours died). An attempt was made to revise the justification used. A number of committee members who commented suggested that a benchmark dose be used to select the point of departure. A benchmark dose analysis was performed below on the BASF (1995) data.

3. BENCHMARK DOSE ANALYSIS OF THE BASF (1995) DATA AND DETERMINATION OF THE AEGL-3 POD

The BASF data is presented in Table 1 below.

TABLE 1. Mortality in rats exposed to iron pentacarbonyl for 6 hrs/day for up to 28 days			
Concentration (ppm)		Results	
Test Group ^a	Analytical	Mortality (no. dead/no. exposed)	Comments
0 control	—	0/10	no clinical signs
4	0.1 (0.1±0.01)	0/10	no clinical signs
E	0.3 (0.3±0.01)	0/10	no clinical signs
1	1 (1.00±0.02)	0/10	no clinical signs
2	3 (2.91±0.01)	5/10	one death after first exposure; 50% after two exposures; death occurred within 4 days
3	10 (9.85)	10/10	dead or terminated in extremis after one exposure; deaths occurred within 3 days

^a Group designators as reported in BASF, 1995

Originally 2.91 ppm exposure for 6 hours was taken as the POD. At this exposure 1 of 10 rats died from a single exposure and 4 more died within 4 days after the second exposure. Since death can take 3-4 days, it is not possible to determine whether the 4 additional animals dying would have done so from one exposure or if 2 exposures were necessary.

Given the uncertainty about how many deaths would have occurred from a single exposure to 2.91 ppm, a log-probit benchmark dose analysis was performed (EPA software V 1.3.1) for two different possibilities and the results are presented below. In one case it was assumed only 1 of 10 animals would have died from 1 exposure and in the other case it was assumed that 5 of 10 animals would have died from a single exposure.

TABLE 2. Log-Probit benchmark dose analysis of BASF (1995) rat data using EPA software V 1.3.1		
Endpoint used	Number of animals dying at 2.91 ppm	
	1 of 10	5 of 10
MLE LC ₀₁	2.4 ppm	1.9 ppm
BMDL LC ₀₅	1.7 ppm	0.80 ppm

choose lower value

Since the data do not permit a distinction between the hypotheses that one exposure would have killed 1, 2, 3, 4, or 5 animals, the ~~worst case scenario~~ that one exposure would have killed 5 animals is assumed. The benchmark dose analysis of this scenario gives an MLE LC_{01} of 1.9 ppm and a BMDL LC_{05} of 0.80 ppm. Since there are insufficient data to differentiate between the MLE LC_{01} and the BMDL LC_{05} the more conservative BMDL LC_{05} value of 0.80 ppm would normally have been selected as the POD for the AEGL-3 estimation. However, since 0 of 10 animals exposed to 1 ppm for 28 days died, 1 ppm is a more reasonable POD than 0.8 ppm.

4. SELECTION OF UNCERTAINTY FACTORS FOR DETERMINATION OF THE AEGL-3

Originally an interspecies UF of 10, and an intraspecies UF of 3 was used according to the rationale presented in Section 1 above. The Sunderman et al. data is the only experiment in which 2 species were tested in a comparable manner. They recorded lethality in mice and rats exposed to iron pentacarbonyl at different doses for 30 minutes. These data below are plotted in Figure 2.

TABLE 3. Lethal toxicity of iron pentacarbonyl in rats exposed for 30 minutes		
Exposure concentration (ppm)	Mortality at 3 days	Mortality at 5 days
244	11/12	11/12
195	12/18	15/18
160	12/18	13/18
118	3/12	6/12
86	1/12	4/12

Sunderman et al., 1959

TABLE 4. Lethal toxicity of iron pentacarbonyl in mice exposed for 30 minutes		
Exposure concentration (ppm)	Mortality at 3 days	Mortality at 5 days
470	16/20	20/20
387	15/20	17/20
270	8/20	9/20
204	5/20	5/20

Sunderman et al., 1959

The rat is about 2-3 times more sensitive than the mouse. Since the most sensitive species was used, the most sensitive experiment and conservative choice of data for the POD, an interspecies UF of 3 is reasonable. Using the original intraspecies UF of 3 the combined UF is 10.

5. DERIVATION OF THE AEGL-3 VALUES

Using 1 ppm exposure for 6 hours as the POD for lethality, a total uncertainty factor of 10, a value of $n=1$ (see original TSD) the AEGL-3 values for iron pentacarbonyl are shown in Table 5.

TABLE 5. AEGL-3 Values for Iron Pentacarbonyl					
AEGL Level	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-3 (Lethal)	3.6 ppm	1.2 ppm	0.60 ppm	0.15 ppm	0.075 ppm

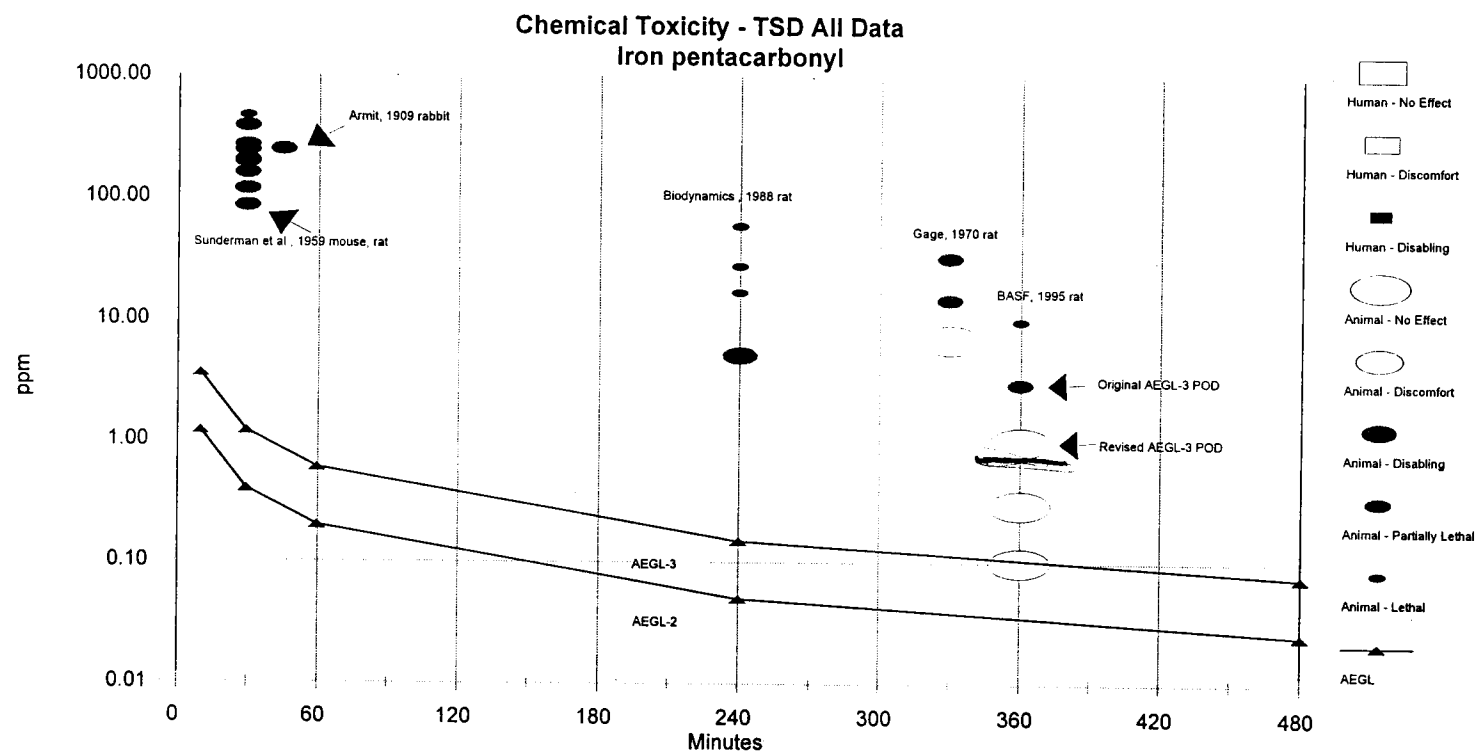
These values are reasonable when viewed against all of the data on iron pentacarbonyl and well below any lethal concentrations in animals. The use of a larger total uncertainty factor would drive AEGL-3 values far below any observed levels of concern.

6. DERIVATION OF THE AEGL-2 VALUES

Using the rationale in the original TSD the AEGL-3 values are divided by 3 to obtain the AEGL-2 values.

TABLE 6. AEGL-2 Values for Iron Pentacarbonyl					
AEGL Level	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-3 (Lethal)	1.2 ppm	0.40 ppm	0.20 ppm	0.050 ppm	0.025 ppm

Figure 1 Category Plot for iron pentacarbonyl



No effect = No effect or mild discomfort

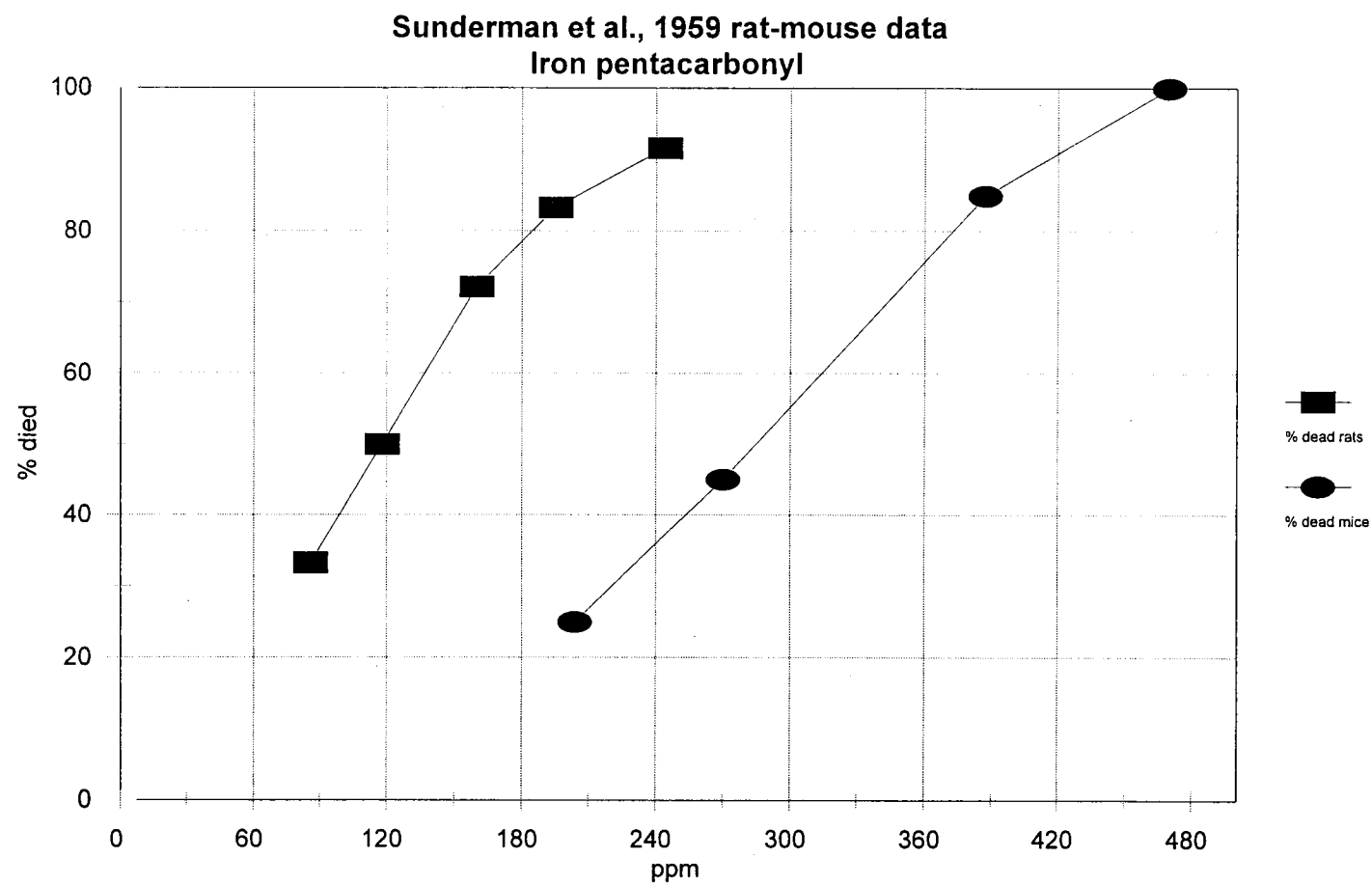
Discomfort = Notable transient discomfort/irritation consistent with AEGL-1 level effects

Disabling = Irreversible/long lasting effects or an impaired ability to escape

Some lethality = Some, but not all, exposed animals died

Lethal = All exposed animals died

Figure 2. Sunderman et al., 1959 rat and mouse lethality data



ACUTE EXPOSURE GUIDELINE LEVELS FOR PIPERIDINE

**PRESENTED BY
KOWETHA DAVIDSON, ORNL,
TOXICOLOGIST**

**MARK MCCLANAHAN,
CHEMICAL MANAGER**

**NAC/AEGL MEETING, SALT LAKE CITY, UT
MARCH 7-8, 2003**

1

PIPERIDINE CAS NO. 110-89-4

PHYSICAL CHARACTERISTICS

- COLORLESS LIQUID
- VAPOR PRESSURE: 32.1 mm Hg @ 25°C; 40 mm Hg @ 29.2°C
- VAPOR DENSITY: 3 (air = 1)
- pH = 12.6 @ 100 g/L, 20°C
- CONVERSION: 1 ppm = 3.48 mg/m³

2

DESCRIPTION

- FLAMMABLE
- EXPLOSIVE VAPORS AT ROOM TEMPERATURE
- STRONG PEPPER- OR AMINE-LIKE PUNGENT ODOR.
- STRONG BASE
- VERY CORROSIVE

3

HUMAN EXPOSURE

- Daily via a large number of food sources
- beverages, candy, baked goods, vegetables, white and black pepper, meats, milk, coffee

HUMAN DATA

- Irritation threshold: 26 ppm
- Odor threshold: <2 ppm

4

ANIMAL DATA

Concentration (ppm)	Duration (minutes)	Clinical Signs	Deaths
20	360	none	none
50	360	nasal irrit. (crusts)	none
80	360	nasal irrit., signs of eye irrit.	none
100	360	nasal irrit (crusts)	none
200	360	nasal irrit., signs of eye irrit.	none
287	240	nasal irrit, eye irrit (reddish secretion)	none
805	240	nasal corrosion, eye irrit., dyspnea	1/20
1178	240	nasal corrosion, cornea damage, dyspnea, CNS toxicity	10/20
1523	240	nasal corrosion, cornea damage, dyspnea, CNS toxicity, prostration	7/20
2167	240	nasal corrosion, cornea damage, dyspnea, CNS toxicity, prostration	20/20

5

AEGL -1 VALUES

Reference: BASF. 1990. Range-finding Study on the Inhalation Toxicity of Piperidin as Vapor in Rats: 5-day Study. Project No. 3010523-89017, BASF Aktiengesellschaft, Ludwigshafen/Rhein, Germany. Unpublished.

Test Species/Strain/Number: male and female rat/Wistar/5 of each sex

Exposure Route/Concentration/Durations: inhalation/ 0, 50, 100, 200 ppm, 6 hours/day, 5 days

Effects: nasal irritation at all concentrations (severity increased with concentration and time); "stretched respiration posture", lid closure, salivation at 200 ppm

Endpoint/Concentration/Rationale: nasal irritation at 50 ppm for 6 hours; lowest concentration at which nasal irritation occurred and there was no involvement of other regions of the respiratory tract

Uncertainty Factors/Rationale: Total uncertainty factor:10

Interspecies: 3, the effects are mediated by direct contact with nasal epithelium, which has similar cellular composition among species although anatomical morphology differs

Intraspecies: 3, the nasal epithelium does not vary among individuals in the population

Modifying Factor: none

Animal to Human Dosimetric Adjustment: none

Time Scaling: default: n =3, scaling to shorter durations; n = 1, scaling to longer durations

AEGL-1 Values for Piperidine

10-minute	30-minute	1-hour	4-hour	8-hour
17 ppm (59 mg/m ³)	11 ppm (38 mg/m ³)	9.1 ppm (32 mg/m ³)	5.7 ppm (20 mg/m ³)	3.8 ppm (13 mg/m ³)

7

AEGL -2 VALUES

Reference: BASF. 1990. Range-finding Study on the Inhalation Toxicity of Piperidin as Vapor in Rats: 5-day Study. Project No. 3010523-89017, BASF Aktiengesellschaft, Ludwigshafen/Rhein, Germany. Unpublished

Test Species/Strain/Number: male and female rat/Wistar/5 of each sex

Exposure Route/Concentration/Durations: inhalation/ 0, 50, 100, 200 ppm, 6 hours/day, 5 days

Effects: nasal irritation at all concentrations (severity increased with concentration and time); "stretched respiration posture", lid closure, salivation at 200 ppm

Endpoint/Concentration/Rationale: nasal irritation along with salivation and evidence of some eye irritation at 200 ppm for 6 hours. The severity of nasal irritation in the rat showed a concentration-related increase, but there was no involvement of other regions of the respiratory tract. The severity at 200 ppm was slightly less than that observed at 287 ppm.

Uncertainty Factors/Rationale: Total uncertainty factor: 10

Interspecies: 3, the effects are mediated by direct contact with nasal epithelium, which has similar cellular composition among species although anatomical morphology differs

Intraspecies: 3, the nasal epithelium does not vary among individuals in the population

Modifying Factor: none

Animal to Human Dosimetric: Adjustment: none

Time Scaling: default: n =3, scaling to shorter durations; n = 1, scaling to longer durations

8

AEGL-2 Values for Piperidine

10 minutes	30 minutes	1 hour	4 hour	8 hour
66 ppm (230 mg/m ³)	46 ppm (160 mg/m ³)	36 ppm (125 mg/m ³)	23 ppm (80 mg/m ³)	15 ppm (52 mg/m ³)

9

AEGL -3 VALUES

Reference: BASF. 1980. Determination of the Acute Inhalation Toxicity LC₅₀ of piperidine as vapor in Sprague-Dawley Rats After a 4-Hour Exposure. BASF Gewerbehygiene und Toxikologie. Unpublished

Test Species/Strain/Number: rats/Sprague-Dawley/10 of each sex

Exposure Route/Concentration/Durations: inhalation/100, 2800, 4100, 5300, and 7540 mg/m³ (287, 805, 1178, 1523, 2167 ppm) for 4 hours (single exposure)

Effects:

1000 mg/m³: - 0/20 deaths, nasal and eye irritation

2800 mg/m³: - 1/20 deaths, nasal and eye irritation, corrosion around the nose (1 rat), dyspnea

4100 mg/m³: - 10/20 deaths, nasal and eye irritation, corneal damage, corrosion around the nose, dyspnea, CNS toxicity

5300 mg/m³: - 7/20 deaths, prostration plus effects noted at 4100 mg/m³

7540 mg/m³: - 20/20 deaths, effects same at 5300 mg/m³

Endpoint/Concentration/Rationale: lethality threshold (LC₀₁) at 1560 mg/m³ (448 ppm). The LC₀₁ approximates the lethality threshold; it is lower than the concentration (2800 mg/m³) where 1 of 20 rats died and had signs of dyspnea, and higher than the concentration (1000 mg/m³) where no deaths occurred and no signs indicate of death were observed.

Uncertainty Factors/Rationale: Total uncertainty factor:10

- Interspecies: 3, The linear correlation for the concentration vs time for LC₅₀ values for three species is -0.96 and the concentration × time relationships are similar, not varying by more than 30%, indicating the response is similar among the three species.
- Intraspecies: 3, an UF of 10 would produce AEGL values for 1, 4, and 8 hours that are lower than the irritation threshold

Modifying Factor: 1**Animal to Human Dosimetric Adjustment:** none**Time Scaling:** default: n =3, scaling to shorter durations; n = 1 for scaling to longer durations.

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AEGL-3 Values for Piperidine

10 minutes	30 minutes	1 hour	4 hour	8 hour
129 ppm (449 mg/m ³)	90 ppm (313 mg/m ³)	71 ppm (247 mg/m ³)	45 ppm (157 mg/m ³)	22 ppm (76 mg/m ³)

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Proposed AEGL Values for Piperidine [ppm (mg/m ³)]						
Classification	10 min.	30 min.	1 hour	4 hours	8 hours	Endpoint/ Ref.
AEGL-1 (Nondisabling)	17 (59)	11 (38)	9.1 (32)	5.7 (20)	3.8 (13)	nasal irritation/ BASF, 1990
AEGL-2 (Disabling)	66 (230)	46 (160)	36 (125)	23 (80)	15 (52)	severe nasal irritation, eye irritation, salivation /BASF, 1990
AEGL-3 (Lethal)	129 (449)	90 (313)	71 (247)	45 (157)	22 (76)	threshold for lethality/ BASF, 1980

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Option 2: AEGL-2 and -3 values for 4- and 8-hour durations are below the reported irritation threshold; propose using the same value for 1-, 4-, and 8-hour durations.

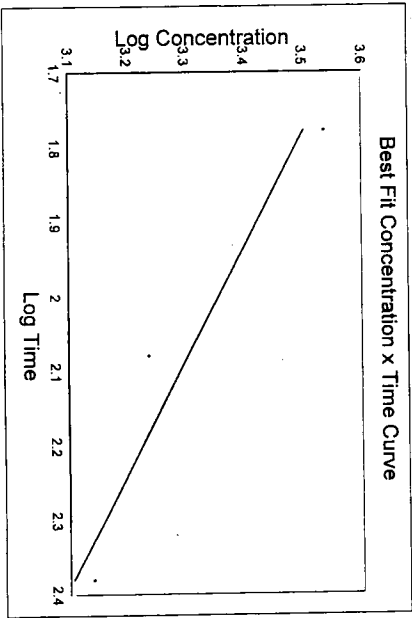
Proposed AEGL Values for Piperidine [ppm (mg/m ³)]						
Classification	10 min.	30 min.	1 hour	4 hours	8 hours	Endpoint/ Reference
AEGL-1 (Nondisabling)	17 (59)	11 (38)	9.1 (32)	5.7 (20)	3.8 (13)	nasal irritation/ BASF, 1990
AEGL-2 (Disabling)	66 (230)	46 (160)	36 (125)	36 (125)	36 (135)	severe nasal irritation, eye irritation, salivation /BASF, 1990
AEGL-3 (Lethal)	129 (449)	90 (313)	71 (247)	71 (247)	71 (247)	threshold for lethality/ BASF, 1980

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Option 3: The effects of piperidine are not dominated by the exposure concentration to the extent indicated by a n = 3 time scaling factor. The data indicate that n=2 would be more appropriate for piperidine.

Proposed AEGL Values for Piperidine [ppm (mg/m ³)]						
Classification	10 min.	30 min.	1 hour	4 hours	8 hours	Endpoint/ Reference
AEGL-1 (Nondisabling)	67 (233)	38 (132)	27 (94)	14 (49)	10 (35)	nasal irritation/ BASF, 1990
AEGL-2 (Disabling)	120 (418)	62 (216)	49 (171)	24 (84)	17 (59)	severe nasal irritation, eye irritation, salivation /BASF, 1990
AEGL-3 (Lethal)	219 (762)	127 (442)	90 (313)	45 (157)	32 (111)	threshold for lethality/ BASF, 1980

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Time	Conc.	Log Time	Log Conc.
60	3444	1.7782	3.5371
120	1724	2.0792	3.2365
240	1379	2.3902	3.1396

Minutes	Conc.	Hours	Conc.
30	5033.70	0.5	75141.23
60	3185.21	1.0	47547.63
240	1275.38	4.0	19038.38
480	807.03	8.0	12047.05

n =	1.51
k =	1.21E+07

Intercept	4.6771
Slope	-0.6602
R Squared	0.9196
Correlation	-0.9590
Degrees of Freedom	5
Observations	7

Regression Output:

Acute Exposure Guideline Levels (AEGLs)

for

Carbon Disulfide (CS₂)

(CAS Reg. No. 75-15-0)

S=C=S

NAC/AEGL-28

March 7-8, 2003

Salt Lake City, Utah

Scientists (Toxicological Consultants):

Jens-Uwe Voss/Gerhard Rosner

Chemical Manager USA:

(George Rodgers)

Chemical Manager in German Expert Group:

Horst Hollander

Chemical Reviewer for German Expert Group:

Helmut Greim/Rüdiger Bartsch

AEGL-1 (agreed on NAC/AEGL -26, Sep 2002)

Key study: Freundt et al. (1976b)

Endpoint: Increase in blood acetaldehyde (1.5 – 2 x control) in humans, no signs of "antabuse syndrome" at exposure to 20 ppm for 8 h

Scaling: $C^n \times t = k$ with default of $n = 3$ for shorter periods of time; $AEGL_{10 \text{ min}} = AEGL_{30 \text{ min}}$ (default for derivation from 8-h-studies and no supporting studies using shorter experiods)

Total uncertainty factor: 10

Intraspecies: 10

The observed increased of blood acetaldehyde levels in normal subjects was not sufficient to cause an "antabuse syndrome". However, population groups (Asian, American Indian) with "low activity" acetaldehyde dehydrogenase (ALDH2(2)) are very sensitive to an "antabuse syndrome" following alcohol intake and could experience reactions or reactions to alcohol (vasodilation with e.g. face flush, pulsating headache, sweating, nausea, hypotension) may be aggravated by exposure to CS₂.

AEGL-1 Values for Carbon Disulfide

10 minutes	30 minutes	1 hour	4 hours	8 hours
5.0 ppm (16 mg/m ³)	5.0 ppm (16 mg/m ³)	4.0 ppm (12 mg/m ³)	2.5 ppm (7.8 mg/m ³)	2.0 ppm (6.2 mg/m ³)

Remark: AEGL-1 is above odor recognition threshold (0.21 ppm; Leonardos et al., 1979) but well below levels reported to cause "moderate odor annoyance" (180-240 ppm; Lehmann, 1894).

AEGL-3 (agreed on NAC/AEGL -26, Sep 2002)

Key studies: Du Pont (1966)

Endpoint: Lethality in rats

3500 ppm, 4 h: 6/6 rats died

3000 ppm, 4 h: 0/6 rats died

Indicating steep concentration-response

"NOEL": 3000 ppm, 4h

Scaling: $C^n \times t = k$, with $n = 3$ for shorter time periods
and $n = 1$ for longer time periods (default)

Total uncertainty factor: 10

Interspecies: 3; because data do not indicate much
variability in acute neurotoxic effects between
species

Intraspecies: 3; because threshold for acute neurotoxic
effects is not expected to vary much in humans

AEGL-3 Values for Carbon Disulfide

10 minutes	30 minutes	1 hour	4 hours	8 hours
600 ppm (1480 mg/m ³)	600 ppm (1480 mg/m ³)	480 ppm (990 mg/m ³)	300 ppm (930 mg/m ³)	150 ppm (470 mg/m ³)

For comparison: "old" values derived from Lehmann (1894)

AEGL-3 Values for Carbon Disulfide

10 minutes	30 minutes	1 hour	4 hours	8 hours
840 ppm (2620 mg/m ³)	840 ppm (2620 mg/m ³)	670 ppm (2080 mg/m ³)	420 ppm (1310 mg/m ³)	330 ppm (1040 mg/m ³)

AEGL-2 to be discussed

Data relevant to AEGL-2

Humans

- Lehmann (1894):
2 male students, controlled static chamber exposure, CS₂ concentrations monitored at about 30 minute intervals, overall concentration range 180 - > 3000 ppm (see Table 2 of TSD draft)

500 ppm, 4 h: dizziness, lacrymation, burning eyes, temporary impairment of reading ability, cough attacks, increased pulse rate, paleness, cold sweat.
- Freundt et al. (1974); Freundt & Lieberwirth (1974b); Mack et al. (1974):

up to 80 ppm: no objective or subjective symptoms noted
- Demus (1964): toxikokinetic study with 10 persons

up to 96 ppm, 8 h; 143 ppm, 5 h: neither symptoms reported nor absence of symptoms explicitly stated; but it may reasonable assumed that severe effects would not have been tolerated in a kinetic study

"Old" values derived from Lehmann (1894)
(proposed September 2002)

AEGL-2 Values for Carbon Disulfide

10 minutes	30 minutes	1 hour	4 hours	8 hours
330 ppm (1040 mg/m ³)	330 ppm (1040 mg/m ³)	260 ppm (820 mg/m ³)	170 ppm (520 mg/m ³)	130 ppm (410 mg/m ³)

Motion in September 2002 (not passed)

83 ppm

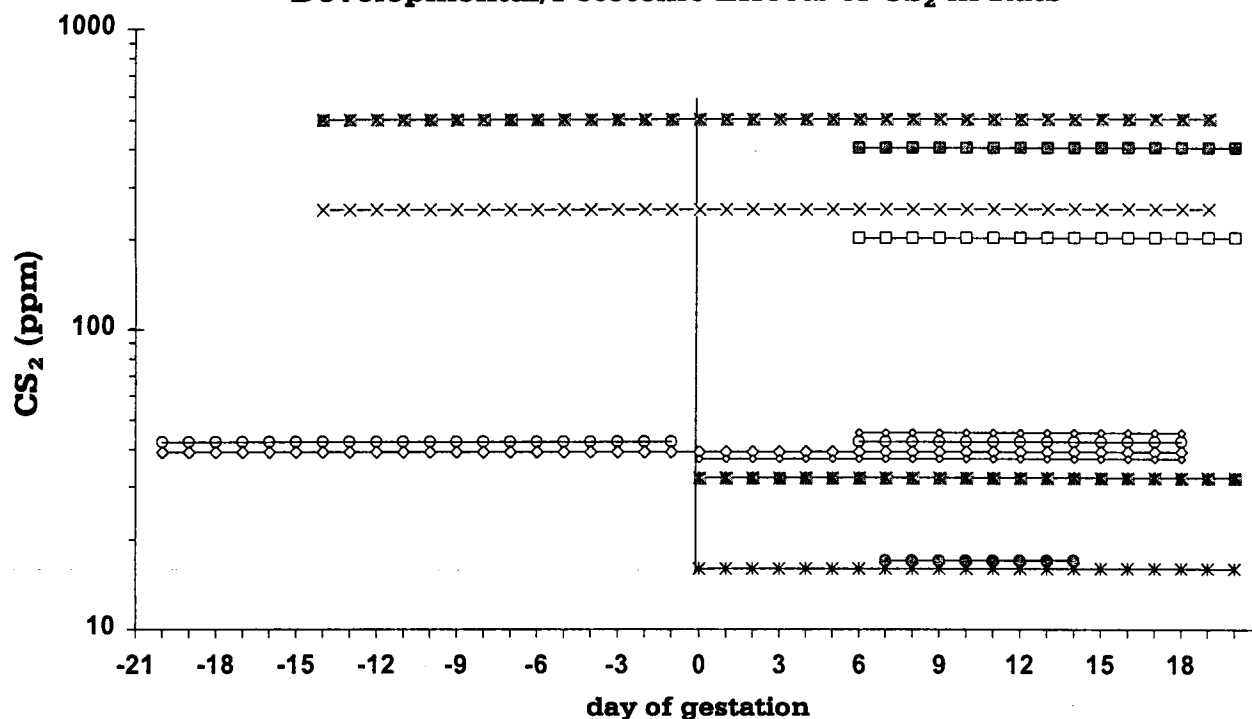
Data relevant to AEGL-2

Animals, single exposure, acute effects

- Weiss et al. (1979)
600 ppm, 2 h: 1 Squirrel monkey
behavioral alterations (altered response to aversive electric shock, elevated aversive threshold indicating anesthetic/analgesic effect)
- Du Pont (1966)
3000 ppm, 4 h 6 rats
tachypnea, ptosis, hyperexcitability, incoordination, gasping
- Goldberg et al. (1964)
2000 ppm, 4 h 8-10 rats
behavioral alterations (inhibition of escape response);

1000 ppm, 4 h no effect after one exposure
- Tarkowski & Sobczak (1971)
800 ppm, 18 h 7 rats
severe narcosis, reduced cardiac/respiratory rate
- Tarkowski & Cremer (1972)
800 ppm, 15 h 6 rats
ataxia, tremor, occasional convulsions
- Tarkowski et al. (1980)
770 ppm, 12 h 7 rats
no visible signs of toxicity reported
- Battig & Grandjean (1964)
800 ppm, 4 h 6 rats
drowsiness shortly after begin of exposure
- Wilmarth et al. (1993)
600 ppm, 10 h 6 rats
narcotic-like stupor
- Kivisto et al. (1979)
500 ppm, 6 h 14 rats
reduced activity level, not strongly irritating or pre-narcotic

Developmental/Fetotoxic Effects of CS₂ in Rats



■ LOAEL 400 ppm (Saillenfait et al. 1989)	□ NOAEL 200 ppm (Saillenfait et al. 1989)
◇ NOAEL 40 ppm (Litton Bionetics 1980)	○ NOAEL 40 ppm (Litton Bionetics 1980)
○ NOAEL 40 ppm (Litton Bionetics 1980)	◇ NOAEL 40 ppm (Litton Bionetics 1980)
■ LOAEL 500 ppm (CMA 1993)	× NOAEL 500 ppm (CMA 1993)
■ LOAEL 32 ppm (Tabacova et al. 1978)	× NOAEL 500 ppm (CMA 1993)
● LOAEL 16 ppm (Yang et al. 1993)	* NOAEL 16 ppm (Tabacova et al. 1978)

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Developmental/Fetotoxic Effects of CS₂ in Rats

Exposure (gestation days)	Effect	NOAEL (ppm)	LOAEL (ppm)	Reference
6 – 20	↓ fetal weight ↓ maternal weight gain ↑ unossified sternebrae ↑ malformations (incl. clubfoot)	200 200 400 800 (h)	400 400 800	Saillenfait et al. 1989
Pre 14 - 0, 0 - 19	↑ pup mortality, dystocia ↓ pup viability, mean litter size	250 250	500 500	CMA 1993
0 – 18 6 – 18 Pre 21 – 0; 0 – 18 Pre 21 – 0; 6 – 18	All groups: no effect on maternal toxicity; no fetotoxicity, no malformations	40 (h) 40 (h) 40 (h) 40 (h)		Litton Bionetics 1980
0 – 21	↑ preimplantation loss ↓ fetal weight (and –gain) ↑ malformations (clubfoot, hydrocephalus)	32 16 16	64 32 32	Tabacova et al. 1978
7 – 14	↑ teratogenic effects (sternum deletion, coronale enlargement; hydrocephalus)		16 (l)	Yang et al. 1993 (in Chinese, English abstract only)

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h: highest; l: lowest concentration

AEGL-2 key study

Goldberg et al. (1964)

Behavior of rats in a pole-climbing test

Avoidance response (conditioned response):
climbing of escape area in response to a
buzzer to avoid electric shock stimulus
within 2 seconds

Escape response (unconditioned response):
climbing of escape area in response to an
electric shock within two seconds

Concentration (ppm)	Days of Exposure (% inhibited)					
	1	2	3	4	5	10
	A* E°	A E	A E	A E	A E	A E
250	0 0	0 0	0 0	0 0	12 0	25 0
500	0 0	0 0	0 0	12 0	25 0	12 0
1000	0 0	0 0	12 0	12 0	25 0	37 0
2000	50 12	50 0	75 25	75 25	88 25	100 62

*: % Group inhibited – Avoidance response

°: % Group inhibited – Escape response

AEGL-2, to be discussed

Key studies: Goldberg et al. (1964)

Endpoint: Neurotoxicity (behavioral alterations in rats)

LOAEL: 2000 ppm, 4 h
(reduced escape response)

NOEL: 1000 ppm, 4h

Scaling: $C^n \times t = k$, with $n = 3$ for shorter time periods
and $n = 1$ for longer time periods (default).

Total uncertainty factor: 10

Interspecies: 3; because data do not indicate much
variability in acute neurotoxic effects between
species

Intraspecies: 3; because threshold for acute neurotoxic
effects is not expected to vary much in humans

AEGL-2 Values for Carbon Disulfide

10 minutes	30 minutes	1 hour	4 hours	8 hours
200 ppm (620 mg/m ³)	200 ppm (620 mg/m ³)	160 ppm (490 mg/m ³)	100 ppm (310 mg/m ³)	50 ppm (160 mg/m ³)

For comparison: "old" values derived from Lehmann (1894)

AEGL-2 Values for Carbon Disulfide

10 minutes	30 minutes	1 hour	4 hours	8 hours
330 ppm (1040 mg/m ³)	330 ppm (1040 mg/m ³)	260 ppm (820 mg/m ³)	170 ppm (520 mg/m ³)	130 ppm (410 mg/m ³)

Motion in September 2003 (not passed)

83 ppm

**SUMMARY TABLE OF AEGL VALUES
FOR CARBON DISULFIDE [ppm (mg/m³)] ^a**

Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1 (Nondisabling)	5.0 (16)	5.0 (16)	4.0 (12)	2.5 (7.8)	2.0 (6.2)
AEGL-2 (Disabling)	200 (620)	200 (620)	160 (490)	100 (310)	50 (160)
AEGL-3 (Lethality)	600 (1480)	600 (1480)	480 (990)	300 (930)	150 (470)

a: Cutaneous absorption may occur. Liquid CS₂ is a severe skin irritant and direct skin contact must be avoided.

ACUTE EXPOSURE GUIDELINE LEVELS
for
FORMALDEHYDE

National Advisory Committee for AEGLs Meeting 27
March 7-8, 2003

ORNL Staff Scientist:
Sylvia S. Talmage

Chemical Manager:
Mark McClanahan

Chemical Reviewers:
George Rusch
George Rodgers

Human Toxicity Data

22 studies with human subjects, over 500 individuals
Addressed eye and upper respiratory tract irritation
Included potentially susceptible populations - asthmatics and sensitized individuals (through dermal contact)
Concentrations ranged from 0.10 to 20 ppm
1 ppm: 129 subjects (healthy, asthmatic, formaldehyde-sensitive)
2 ppm: 49 healthy and asthmatic subjects, some exercising
3 ppm: 107 healthy subjects, 45 asthmatic subjects
exercise incorporated into some protocols
4-5 ppm: ~100 healthy subjects
8, 13, 13.8 ppm: 22 healthy subjects
20 ppm: 2 healthy individuals

Exposure periods ranged from few minutes to 5.5 hours
adaptation to the eye irritation

Human Toxicity Data (cont'd)

Effects: only upper respiratory tract irritation - up to 3 ppm
<1 ppm: some eye, nose, throat irritation noted,
but no dose-response
1 ppm: threshold for eye irritation (slight)
no changes in pulmonary function parameters
2 ppm: mild to moderate eye, nose, throat irritation
no change in symptoms with exercise
no changes in pulmonary function parameters
no asthmatic response
3 ppm: mild to moderate eye, nose, throat irritation
no/slight changes in pulmonary function parameters
healthy individuals engaged in heavy exercise
no asthmatic response during/following exercise

Human Toxicity Data (cont'd)

4, 5 ppm: little eye irritation in one study, severe in second study
8, 13, 14 ppm: little eye irritation at 8 ppm
eye irritation at 13 ppm
13.8 ppm: nasal, eye irritation with mild lacrimation
adaptation to the eye irritation
20 ppm: nose, throat, eye irritation with lacrimation
considered objectionable

Concentrations up to 3 ppm scrubbed in the anterior nasal passages
no bronchoconstriction in asthmatic subjects

Animal Studies

Target is the nasal respiratory epithelium

Sublethal Effects

Most studies at sublethal concentrations were chronic
addressed carcinogenicity

2 ppm: chronic NOAEL - nasal epithelial lesions

Acute Exposures

Rat: 2 ppm for 6 hours - minimal signs of eye, nose irritation
no epithelial lesions (Morgan et al. 1986a, 1986b)

6 ppm for 6 hours - 15% decrease in respiratory rate
(Chang et al. 1983)

6 ppm for 6 hours - nasal lesions
(Morgan et al. 1986a, 1986b)

10 ppm for 6 hours - no signs (Tobe et al. 1985)

15 ppm for 90 minutes or 6 hours
severe degenerative changes of nasal epithelium
recovery if sacrifices delayed 1 hour
(Morgan et al. 1986a, 1986b; Chang et al. 1983)

Animal Studies (cont'd)

Mouse

3.1 ppm - RD_{50} (Kane and Alarie 1977)

Guinea pig

0.31 ppm for 1 hour: bronchoconstriction

11 ppm: decrease in respiratory rate and minute ventilation
(Amdur 1960)

Lethal Concentrations

Rat:

140 ppm: 2 hours/4 days, few signs of distress (Horton et al. 1963)

820 ppm: 30-minute LC_{50} (Skog 1950)

482 ppm: 4-hour LC_{50} (Nagorny et al. 1979)

350 ppm - no deaths

Mouse:

410 ppm: 2-hour LC_{50} (Nagorny et al. 1979)

98 ppm - no deaths

Animal Studies (cont'd)

Developmental/Reproductive Toxicity (Saillenfait et al. 1989)

Rat: 20, 40 ppm, g.d. 6-20: reduced fetal body weights
maternal toxicity
not teratogenic

Genotoxicity: genotoxic in a variety of systems

Carcinogenicity: carcinogenic in rat following chronic exposures

site-specific - nasal respiratory epithelium
mechanism - cytotoxicity and DNA-protein cross-links
low carcinogenicity in mice
not carcinogenic in hamsters

Derivation of AEGL-1

Weight of evidence from 22 human studies:

look at ALL of the studies
endpoint is eye, nose, throat irritation
variability in response

<1 ppm: no clear concentration-response for irritation

1 ppm: threshold for eye irritation, generally rated slight (IHFP)

3 ppm: mild to moderate eye irritation (152 subjects)

no to slight decrements in pulmonary parameters
healthy and asthmatic subjects tested

subjects were exercising which increases respiratory rate/uptake

3 ppm: NOAEL for definition of an AEGL-1 - notable discomfort
intraspecies uncertainty factor of 3 sufficient:
non-sensitive subjects excluded from one study

Derivation of AEGL-2

Two clinical studies

Endpoint is eye, nose, and throat irritation

8 ppm: no eye irritation for 4 of 5 subjects (Douglas 1974)

13 ppm: eye irritation for 5 of 6 subjects (Douglas 1974)

increase in airway "conductance," but administration via mouth

13.8 ppm: mild lacrimation with adaptation (Sim and Pattle 1957)

eye irritation not considered severe (12 subjects)

8 ppm: NOAEL for eye irritation severe enough to impede escape

Interspecies uncertainty factor of 1: a larger uncertainty factor would reduce the value to a no-effect concentration in exercising asthmatics

Time-scaling: use same value across exposure durations because adaptation occurs to the irritation

Classification	Exposure Duration				
	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1	1 ppm	1 ppm	1 ppm	1 ppm	1 ppm
AEGL-2	8 ppm	8 ppm	8 ppm	8 ppm	8 ppm
AEGL-3 Skog 1950 Nagorny et al. LC ₅₀ no deaths	108 ppm	75 ppm	59 ppm	24 ppm	24 ppm
	118 ppm	82 ppm	41 ppm	10 ppm	5 ppm
	138 ppm	96 ppm	76 ppm	48 ppm	24 ppm
	127 ppm	88 ppm	70 ppm	35 ppm	18 ppm

820

350 / 482

Derivation of AEGL-3

Sublethal and lethal studies with rats; no data to calculate LC₀₁

Consistent values among three studies:

140 ppm: 2 hours/4 days, few signs of distress (Horton et al. 1963)

820 ppm: 30-minute LC₅₀ (Skog 1950)

482 ppm: 4-hour LC₅₀ (Nagorny et al. 1979); no deaths: 350 ppm

140 ppm for 2 hours in repeat study: NOAEL for lethality

Divide by single interspecies factor of 3 = 2-hour AEGL-3 of 47 ppm

uptake more rapid/greater in the rodent compared with humans

a greater interspecies uncertainty factor (10) or addition of an

intraspecies uncertainty factor (3) reduces the value to 14 ppm -

produced only mild lacrimation in humans (Sim and Pattle 1957)

Divide 30-minute LC₅₀ by 10 = 82 ppm

Divide 4-hour LC₅₀ by 10 = 48 ppm

Time-scaling: no data, default values of n = 1 and 3

usually results in 8-hour values that are too low

reasons: formaldehyde well scrubbed, occupational values

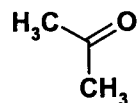
1050

Acute Exposure Guideline Levels (AEGLs)

for

Acetone

(CAS Reg. No. 67-64-1)



NAC/AEGL-28, March 7-8, 2003

Salt Lake City, Utah

Scientists (Toxicological Consultants):

Jens-Uwe Voss/Gerhard Rosner

Chemical Manager USA:

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Chemical Manager in German Expert Group:

Rudolf Jäckh

Chemical Reviewer for German Expert Group:

Ursula Gundert-Remy

NAC/AEGL-28; March 2003

1

Acetone

Properties

- colorless liquid
- odor sweetish, mildly pungent and fruity,
wide range of odor detection thresholds
3.6 – 653 ppm, geom. mean 62 ppm (AIHA 1997)
41 – 86 ppm (Dalton et al. 1997a, 2000;
Wysocki et al. 1997)
- high vapor pressure, low flash point, lower range of
explosive limits in air: 2.6 %:
→ fire and explosion hazard.

Production - Capacity about 3.8 million tons (1994)

- peroxidation of cumene and cleavage of cumene
hydroperoxide to acetone and phenol (96 % of total),
- oxidation of isopropanol, other processes (4 % of total).

Use

- most widely used ketone: as solvent, syntheses of
methacrylates, bisphenol A, other ketones.

Toxicity mechanism and concerns

- acute:
 - irritation of eyes and mucous membranes,
 - central nervous system (CNS) depression
- (chronic:
 - effects on kidney, liver, testes,
 - developmental effects.)

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2

Data relevant to AEGL-1

Humans

Exposure duration	Conc. (ppm)	No. of subjects, effects and remarks	Ref.
3 - 5 minutes	200 300 500	10 subjects of both genders Judged satisfactory for 8-hour exposure Slight irritation (not further specified). Irritating to eyes, nose and throat in most subjects; judged objectionable for 8-hour exposure	Nelson et al. 1943
2 hours	250	10 male subjects No increased ratings of discomfort, i.e. of irritative symptoms in eyes or airways or effects on the CNS such as headache, fatigue, feeling of sickness, dizziness	Ernstgard et al. 1999
6 hours (45 min. break after 3 hours)	100 or 250 500 or 1000	5 male subjects (i) Slight mucous membrane irritation; (ii) unpleasant odor; (iii) morning after complaints: feeling of tension, heavy eyes, lack of energy at 250 ppm; none at 100 ppm Above signs and symptoms more pronounced	Matsushita et al. 1969a
20 min.	800	27 workers: odor rated as weak-to-moderate, 32 non-occupationally exposed subjects: odor rated as strong-to-very strong; decreasing odor intensity with time; perceived irritation intensity correlated with corresponding odor results 90 subjects with no history of occupational exposure to solvents: Positive bias resulted in lower levels of perceived odor intensity, irritation and health symptoms	Dalton et al. 1997a; Dalton et al. 1997b

Exposure duration	Conc. (ppm)	No. of subjects, effects and remarks	Ref.
4 hours	1000	16 male subjects; subjective mucosal irritation on eyes, mouth and throat; subjective symptoms of complaints and annoyance; no significant effects on behavioral parameters	Seeber et al. 1992b
4 hours; 8 hours	1000	2 x 16 male subjects; subjective mucosal irritation (continuously decreasing with 8 hours exposure); no significant effects on behavioral parameters	Seeber and Kiesswetter 1991
3 or 7.5 hours (4 days/week)	0, 200, 1000, 1250	4 male subjects; increase in visual evoked response at 1250 ppm (7.5 hours); 1000, 1250 ppm: slightly more complaints of eye and throat irritation and tiredness as compared to control sessions	Stewart et al. 1975
8 hours	2110 (at rest or moderate exercise)	Subjects not otherwise specified; no indication of "intoxication"	Haggard et al. 1944
15 min. 5 minutes	4600 9300	1 subject; not tolerable longer than 15 min. due to throat irritation not tolerable longer than 5 min. due to severe throat irritation	Kagan 1924
short "sniffs"	36,669 ppm 15,758 ppm 36,608 ppm	chemesthetic lateralization threshold median in 27 occupationally exposed median in 32 nonoccupationally "naïve" median in 40 nonoccupationally "naïve"	Dalton et al. 1997a; 2000

Data relevant to AEGL-1

Animals

Species (strain, no.)	Conc. (ppm)	Exposure Duration	Effect	Ref.
Mouse (Swiss OF-1, 6)	23,480	5 minutes	RC ₅₀ for sensory irritation	de Ceaurriz et al. 1981
Mouse (Swiss-Webster, 4)	77,516	10 minutes	RC ₅₀ for sensory irritation	Kane et al. 1980
Guinea pig (1)	21,800	0.4 hours	Slight lacrimation	Specht et al. 1939
Cat (1)	1055 or 2442	5 hours	Slight lacrimation and salivation	Kagan 1924
Cat (2 – 3 animals)	16,840	4 hours	Eye irritation; ataxia after 1.5 hours	Flury and Wirth 1934

AEGL-1

Key studies: Ernstgard et al. 1999; Matsushita et al. 1969a; Nelson et al. 1943; Stewart et al. 1975

Endpoint: **200 ppm:** subjective symptoms (irritation) not reported more often than in controls (Nelson et al., 1943; Stewart et al. 1975);

250 ppm: slight irritation, few complaints about discomfort in one study (Matsushita et al. 1969a) but not in another (Ernstgard et al. 1999)

300 ppm: slight irritation in majority of volunteers (Nelson et al. 1969);

Scaling: one value for all time points since local effect, accommodation, complaints about discomfort not reported to increase during several hours of exposure

Total uncertainty factor: 1

Intraspecies: 1

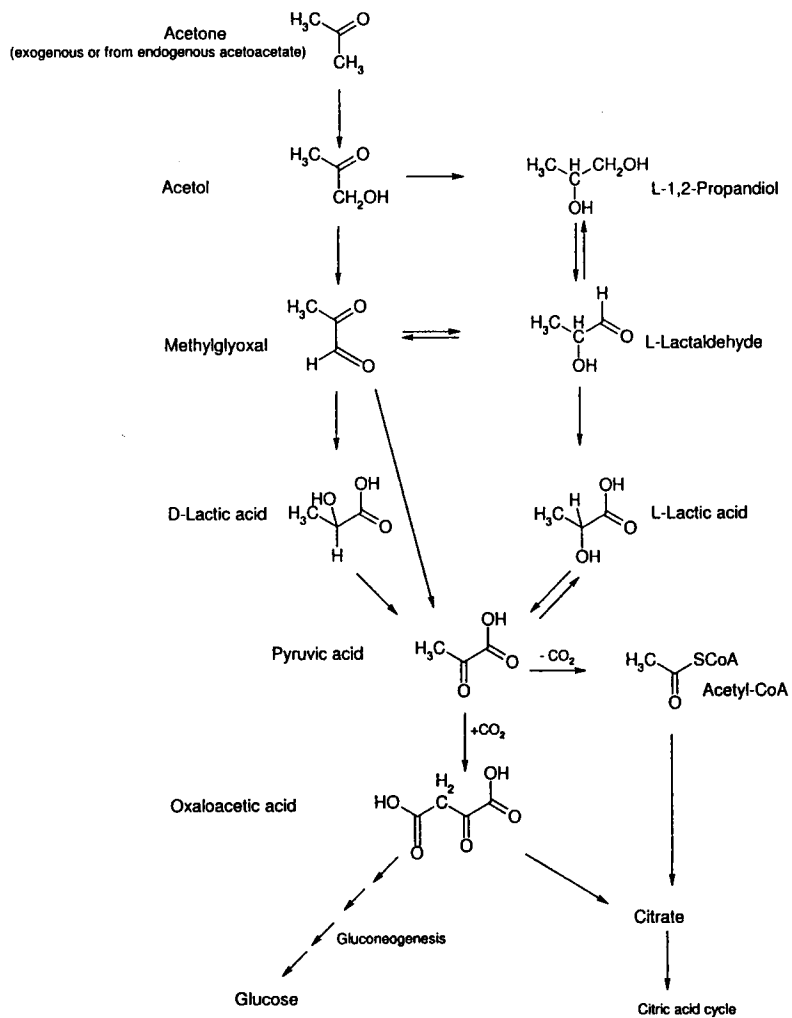
200 ppm as NOEL for local effects, effects weak at higher concentrations

AEGL-1 Values

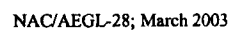
10 minutes	30 minutes	1 hour	4 hours	8 hours
200 ppm (470 mg/m ³)	200 ppm (470 mg/m ³)	200 ppm (470 mg/m ³)	200 ppm (470 mg/m ³)	200 ppm (470 mg/m ³)

Remark: AEGL-1 is above odor recognition threshold.

Data relevant to AEGL-2



Pathways for the metabolism of acetone (after Kalapos 1999)



Data relevant to AEGL-2

Humans

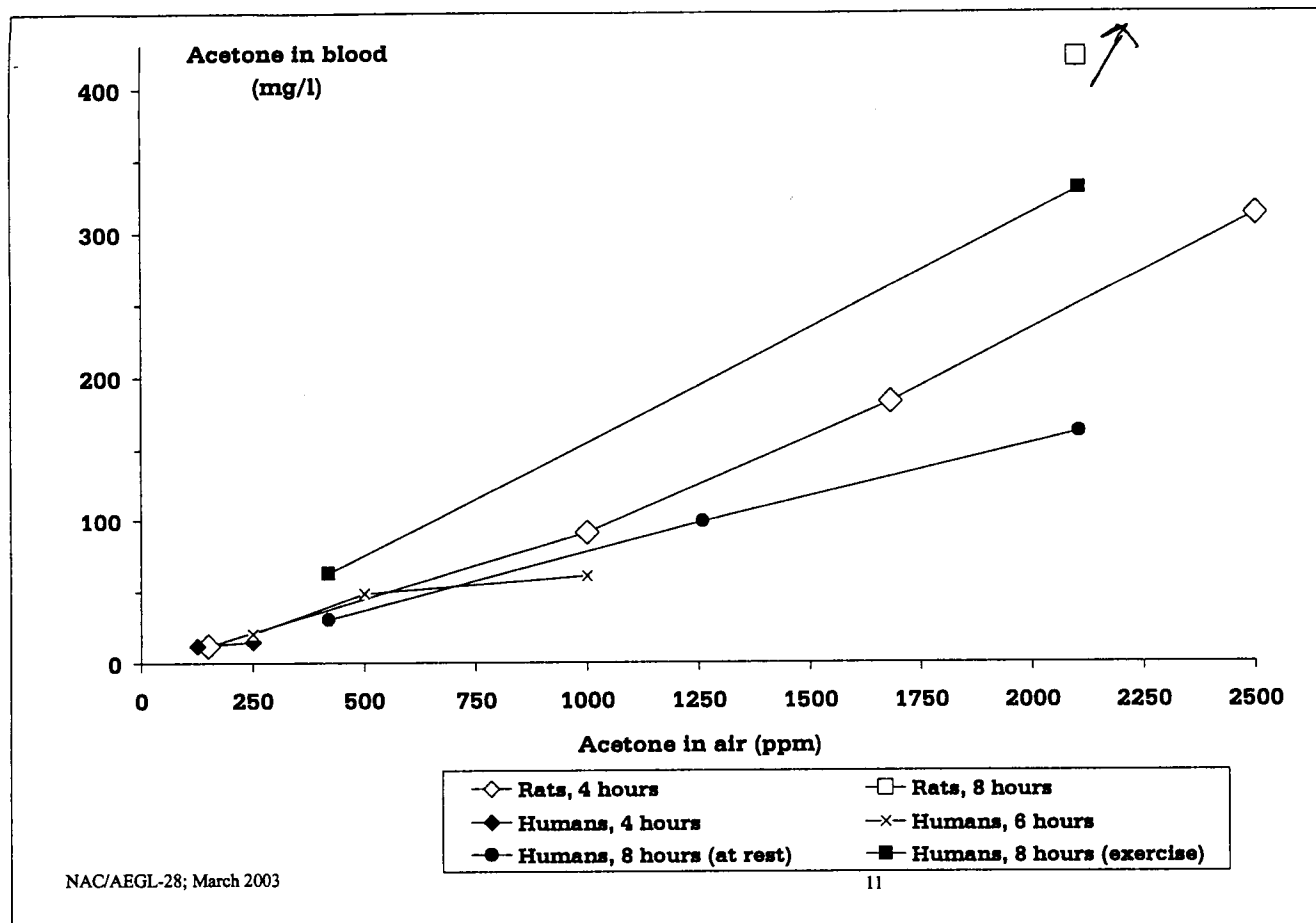
EXPOSURE, BLOOD LEVEL AND EFFECTS OF ACETONE IN HUMANS

Expo- sure time	Conc. in air (ppm)	Conc. in venous blood (mg/L) ^a	Effects/Remarks	Ref.
		< 10 100 - 700	Upper limit in <u>non-fasting</u> healthy humans; range in ketoacidotic diabetics	IOMC 2000
		44 (27 - 84) 17 (11 - 27) 80 (60 - 98)	Mean value (range) in 6 non-obese, 6 obese humans after fasting 3 d; 3 obese humans after fasting 21 d	Reichard et al. 1979
0 hours 2 hours 4 hours	-- 125 125	ca. 2.0 6.2 10.4 / ca. 12	Pre-exposure level No effect in neurological tests; Males /Females	Brown et al. 1987; Dick et al. 1988
2 hours 4 hours	250 250	9.0 15.3	Questionable effects on few parameters in neurological tests	Brown et al. 1987; Dick et al. 1988
2 hours	100 500	ca. 2 ca. 10	No subjective symptoms noted	Di Vincen- zo et al. 1973
2 hours	250	16.8	Value at light exercise (50 W); no subjective symptoms noted	Ernstgard et al. 1999
0.5 hours 0.5 hours 2 hours	300 550 550	3.6 4.3 9.9	Values for resting subjects	Wigaeus et al 1981
6 hours	250 500 1000	ca. 20 ca. 48 60	Subjective symptoms next morning: slight feeling of tension, heavy eyes, lack of energy	Matsushit a et al. 1969a
2 hours		140 / 195 ca. 230	Mean values for 7 and 19 healthy for 12 diabetics after i.v. infusion of 10 g acetone/200 ml saline at over 2 hours (83 mg/minute); slight drop in blood pressure and slight temporary drowsiness	Koehler et al. 1941

EXPOSURE, BLOOD LEVEL AND EFFECTS OF ACETONE IN HUMANS

Expo- sure time	Conc. in air (ppm)	Conc. in venous blood (mg/L) ^a	Effects/Remarks	Ref.
8 hours	420 1260 2105	30 99 162	Resting subjects; no signs of intoxication noted	Haggard et al. 1944
8 hours	420 2105	62 330	At moderate exercise, no signs of intoxication noted	Haggard et al. 1944
		ca. 70 (2 h after intake)	Oral intake of ca. 80 mg/kg b.w. by volunteer; no adverse effects noted	Haggard et al. 1944
		436 (8 h after accident) 302 (10 h) 180 (next day)	Accidental inhalation at work, man hospitalized unconscious, medical treatment, recovery	Sack 1941
		2000 (several h after intake) 400 (one d later)	Oral intoxication (pure acetone), man hospitalized unconscious, respiratory insufficiency, medical treatment, recovery	Zettinig et al. 1997
		2500 (at admission to hospital)	Oral intoxication, hospitalized lethargic, minimally responsive; medical treatment, recovery	Ramu et al. 1978
		4450 (1 h after onset of symptoms) 2650 (18 h) 420 (48 h) 40 (72 h)	Oral intoxication (mixture of 65 % acetone and 10 % isopropanol), child 2½ a, effects: seizure, unconsciousness, no arousal to pain, respiratory depression, acid- osis; medical treatment, recovery	Gamis and Wasser- man 1988

a: at end of exposure time, if not otherwise stated.



Data relevant to AEGL-2				
Animals				
Species (strain, no.)	Conc. (ppm)	Exposure Duration	Effect	Ref.
Rat (CFE, f, 8-10)	3000 6000 12,000 or 16,000	4 h/d, up to 10 days	None no ataxia ataxia the first day; escape response inhibited on day 1, avoidance response on day 1 - 10	Goldberg et al. 1964
Rat (SD, m, 5)	12,600 19,000 25,300	3 hours 3 hours 3 hours	Definite ataxia with impaired locomotion animals immobile in absence of stimulation, recovery after 9 hours hypnosis with arousal difficult	Bruckner and Peterson 1981a
Rat (n.o.s.)	2105 4210 10,525 21,050 42,100 42,100 84,200 84,200 126,300 126,300	8 h 8 h 1.7-4.2 h 2.2-2.7 h 1.75-1.9 h 4.5-5.5 h 0.35-0.83 h 2.5-3 h 0.17-0.42 h 1.75-2.25 h	None none incoordination loss of righting reflex loss of corneal reflex respiratory failure loss of corneal and righting reflex respiratory failure loss of corneal and righting reflex respiratory failure	Haggard et al. 1944
Mouse (CD-1; f; 32)	11,000 6,600	6 h 6 h/d; 12 d	Severe narcosis, no deaths No overt signs of toxicity	NTP 1988
Mouse (CD-1, m, 12)	<1000 3200 10,694 (±2738) 30,000 56,000	30 minutes 30 minutes 30 minutes 30 minutes 30 minutes	None EC ₁₀ : decreased response in operant behavioral test EC ₅₀ : decreased response in operant behavioral test Responding ceased in most mice Responding ceased in all mice	Glowa and Dews 1987
NAC/AEGL-28; March 2003				

Species (strain, no.)	Conc. (ppm)	Exposure Duration	Effect	Ref.
Mouse (white, 2- 4)	8420 20,208 54,730	7.8 hours 1.6 hours 0.7 hours	Ataxia after 1.6-2.3 hours; drowsiness after 3.9-7.7 hours deep narcosis in 3/4 animals after 0.7-1.2 hours deep narcosis in 4/4 animals after <0.7 hours	Flury and Wirth 1934)
Guinea pig (f, 10)	21,800	0.4 hours 4 hours 8.4 hours 9 hours	Slight lacrimation ataxia drowsiness (8), no auditory reflex (2), narcosis (2) narcosis (9), no auditory reflex (2), poor righting reflex	Specht et al. 1939
Cat (n.o.s., 1)	1055 or 2442 3747 5094 7620 13,472; 21,892; 52,625	5 hours 4.5 hours 4 hours 4.5 hours 3.5; 3.7; 1.3 hours	Slight lacrimation and salivation Slight drowsiness and stupor Drowsiness, ataxia Narcosis with clonic convulsions Deep narcosis with clonic convulsions	Kagan 1924
Cat (f+m, 2-3)	16,840 48,468 74,938	3.75-4 hours 1.8 hours 1.1 hours	Eye irritation; ataxia after 1.5 hours; drowsiness after 3.7 hours narcosis narcosis with clonic convulsions	Flury and Wirth 1934)
NAC/AEGL-28; March 2003				

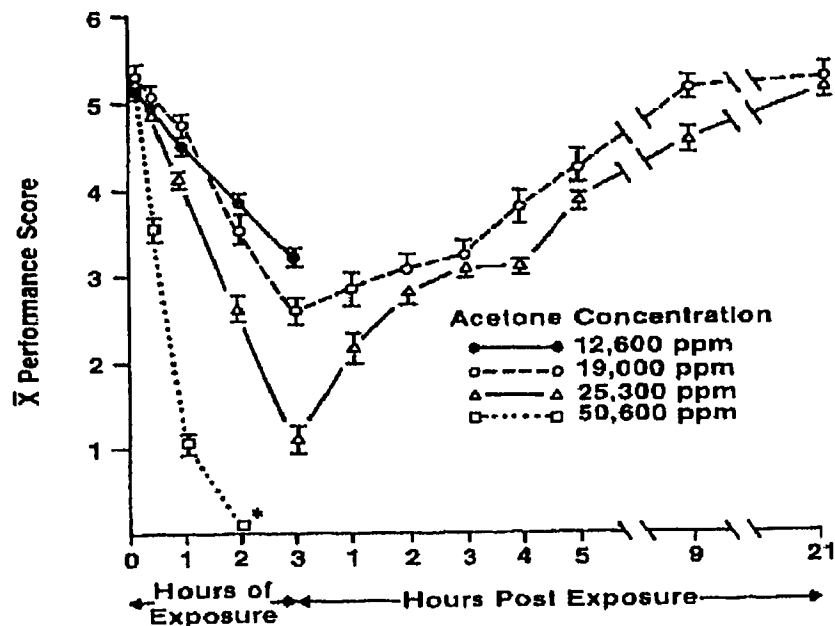
Goldberg et al. (1964)

Concentration (ppm)	Days of Exposure (% inhibited)									
	1		2		3		4		5	
	A*	E°	A	E	A	E	A	E	A	E
3,000	0	0	0	0	0	0	0	0	0	0
6,000	38	0	25	0	0	0	0	0	0	0
12,000 *	50	12	37	0	25	0	0	0	0	0
16,000 *	62	25	37	0	37	0	25	0	25	0

* % Group inhibited Avoidance response; °: Escape response

#: Ataxia in several animals after one exposure

Bruckner et al. (1981)



AEGL-2

Key studies: Goldberg et al. (1964);
Bruckner and Peterson 1981a

Endpoint: Effects on CNS in rats

LOAEL: 12000 ppm, 4 h;
12600 ppm, 3 h
(ataxia, reduced escape response)

NOEL: 6000 ppm, 4h

Scaling: $C^n \times t = k$, with $n = 3$ for shorter time periods
and $n = 1$ for longer time periods (default).

Total uncertainty factor: 3

Interspecies: 1; because data do not indicate much
variability in toxikokinetics and in acute
neurotoxic effects between species;

factor of 3 incompatible with human data
(total UF = 10 would give
4-h AEGL-2: 600 ppm; 8-h AEGL-2: 300 ppm)

Intraspecies: 3; because threshold for acute CNS effects
is not expected to vary much in humans

AEGL-2 Values

10 minutes	30 minutes	1 hour	4 hours	8 hours
4000 ppm* (9500 mg/m ³)	4000 ppm* (9500 mg/m ³)	3200 ppm* (7500 mg/m ³)	2000 ppm (4700 mg/m ³)	1000 ppm (2400 mg/m ³)

*: Values higher than 1/10 of lower explosive limit in air (2.6 %).

Alternative: time scaling to 10 minutes:

5800 ppm*
(13700 mg/m³)

Data relevant to AEGL-3

Animal

Species	Con. (ppm)	Exposure Duration	Effect	Reference
Rat	16,000	4 h	Death in 1/6 animals	Smyth et al. 1962
Rat	32,000	4 h	LC ₁₀₀ (death in 6/6 animals)	Smyth et al. 1962
Rat	21,092	8 h	LC ₅₀	Pozzani et al. 1959
Rat	31,996	4 h	LC ₅₀	Pozzani et al. 1959
Rat	50,600	2 h	Lethal after 2 hours (5 rats exposed, no. of deaths not reported)	Bruckner and Peterson 1981a
Rat	55,700	3 h	LC ₅₀	Bruckner and Peterson 1981a
Mouse	46,310	1 h	Deep narcosis; death in 2/3 animals after 6-10 minutes	Flury and Wirth 1934
	54,730	0.7 h	deep narcosis, no deaths	
Mouse	63,150	2 h	LC ₅₀ (no details reported)	Izmerov et al. 1982
Guinea pig	50,000	3-4 hours	Death in 8/8 animals; pulmonary congestion, edema, glomerular distension	Specht et al. 1939
Cat	21,260	3 hours	Death in 1/1 animals	Kagan 1924
	26,944	4 hours	Death in 1/1 animals	
Cat	74,938	1.1 hours	No deaths	Flury and Wirth 1934

AEGL-3

Key studies: Smyth et al. (1962):
Death in 1/6 animals following exposure to 16,000 ppm 4 hours

Bruckner and Peterson 1981a:
No lethality in rats following exposure to 12,600 ppm for 3 hours

Endpoint: No lethality in rats at 12,600 ppm, 3 hours

Scaling: $C^n \times t = k$ with $n=3$ for shorter periods of time and $n=1$ for longer periods of time

Total uncertainty factor: 3

Interspecies: 1 (see AEGL-2);
factor of 3 incompatible with human data
(total UF = 10 would give
4-h AEGL-3: 950 ppm; 8-h AEGL-2: 470 ppm)

Intraspecies: 3

Because the threshold for acute neurotoxic effects on the CNS is not expected to vary much in humans

AEGL-3 Values Acetone

10 minutes	30 minutes	1 hour	4 hours	8 hours
7600 ppm* (18000 mg/m ³)	7600 ppm* (18000 mg/m ³)	6100 ppm* (14000 mg/m ³)	3200 ppm* (7500 mg/m ³)	1600 ppm (3700 mg/m ³)

*: Values higher than 1/10 of lower explosive limit in air (2.6 %).

Alternative: time scaling to 10 minutes:

11,000 ppm*
(26,1000
mg/m³)

**SUMMARY TABLE OF AEGL VALUES
FOR ACETONE [ppm (mg/m³)] ***

Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1 (Nondisabling)	200 ppm (470 mg/m ³)	200 ppm (470 mg/m ³)	200 ppm (470 mg/m ³)	200 ppm (470 mg/m ³)	200 ppm (470 mg/m ³)
AEGL-2 (Disabling)	4,000 ppm* (9,500 mg/m ³)	4,000 ppm* (9,500 mg/m ³)	3,200 ppm* (7,600 mg/m ³)	2,000 ppm (4,700 mg/m ³)	1,000 ppm (2,400 mg/m ³)
AEGL-3 (Lethality)	7,600 ppm* (18,000 mg/m ³)	7,600 ppm* (18,000 mg/m ³)	6,100 ppm* (14,000 mg/m ³)	3,200 ppm* (7,500 mg/m ³)	1,600 ppm (3,700 mg/m ³)

a: Cutaneous absorption of liquid acetone may occur. Since liquid acetone is an eye irritant, eye contact must be avoided.

*: Concentrations are higher than 1/10 of the lower explosive limit of acetone in air (2.6 % = 26,000 ppm). Therefore, safety considerations against hazard of explosion must be taken into account.

Alternative: time scaling to 10 minutes:

AEGL-1 (Nondisabling)	200 ppm (470 mg/m ³)
AEGL-2 (Disabling)	5,800 ppm* (13,700 mg/m ³)
AEGL-3 (Lethality)	11,000 ppm* (26,100 mg/m ³)

Alternative AEGL-3

Key studies:

Bruckner and Peterson 1981a: rats

score 3-4: definite ataxia with difficulty in locomotion

2-3: animals immobile in the absence of stimulation

1-2: hypnosis with arousal difficult

at or below 1: unconsciousness

12,600 ppm 3 hours: score 3 – 4

19,000 ppm 3 hours: score 2 – 3, recovery

25,300 ppm 3 hours: score just above 1 (as score at 50,600 ppm, 1 h), the standard errors presented indicate that unconsciousness occurred; recovery

50,600 ppm after 1 hour score just above 1, death after 2 hours

Kagan 1924, Flury and Wirth 1934: cats

13,470 ppm 3 h severe narcosis with loss of reflexes (righting, cornea and pupil reflex), no death

21,852 ppm 3 h as above, clonic convulsions, no death

21,260 ppm 3 h as above, death on 3rd morning after end of exposure (2 weeks or more before, this animal had been exposed to 13470 ppm – see above)

26,944 ppm 4 h symptoms as above, death next morning

52,625 ppm 80 min loss of righting reflex, deep narcosis, recovery

16,480 ppm ca. 4 h loss of righting reflex, choking (retching) and vomiting frequently occurred loss of righting.

Endpoint: Severe life-threatening effects at concentrations exceeding 19,000 ppm

NOEL: 19,000 ppm, 3 h

Scaling: $C^n \times t = k$ with $n=3$ for shorter periods of time and $n=1$ for longer periods of time

Total uncertainty factor: 3

Interspecies: 1 (see above)

Intraspecies: 3

Because the threshold for acute neurotoxic effects on the CNS is not expected to vary much in humans

AEGL-3 Values

10 minutes	30 minutes	1 hour	4 hours	8 hours
11,500 ppm* (27,000 mg/m ³)	11,500 ppm* (27,000 mg/m ³)	9100 ppm* (22,000 mg/m ³)	4800 ppm* (11,000 mg/m ³)	2400 ppm (5700 mg/m ³)

*: Values higher than 1/10 of lower explosive limit in air (2.6 %).

Alternative: time scaling to 10 minutes:

17,000 ppm*
(40,000 mg/m³)

Level of Distinct Odor Awareness

Values for "naïve" (not occupationally exposed) volunteers

Substance	Odor detection threshold (ppm)			Ref.
	Median	75 th /25 th ratio	Mean (SEM)	
n-Butanol	0.16	139-fold	2.97	Wysocki et al. 1997
	0.20	40-fold	2.72 (1.04)	Dalton et al. 1997a °
	0.25	31-fold	5.23 (4.70)	Dalton et al. 1997b *
	0.26	83-fold	5.20 (2.73)	Dalton et al. 1997b #
Acetone	41	26-fold	247	Wysocki et al. 1997
	83.9	45-fold	395.3 (131.2)	Dalton et al. 1997a °
	53.4	37-fold	306.7 (119)	Dalton et al. 1997b *
	135.9	22-fold	264.0 (74.8)	Dalton et al. 1997b #

°: same values as "neutral bias group in Dalton et al. 1997b; *: "negative bias group"; #: "positive bias group"; differences not statistically significant

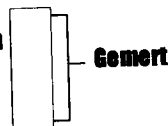
- Wysocki et al. (1997):
 - Values determined with up-to-date method ("two-alternative, forced-choice, modified staircase", "method of choice for most ... applications since it provides a reliable threshold measure...")
 - No correlation between acetone and butanol olfactory thresholds
- No calculation of corrected odor threshold (butanol reference odor threshold would be 0.04 ppm),
- Take lowest value from table: 41 ppm
- Level of Distinct Odor Awareness:
41 ppm x 16 (default) = 660 ppm

Discussion Topics

- **Odor LOA? Some inherent warning?**
 - Hori (vs. Gemert)
- **AEGL Committee request at Sept. 2002 Meeting:**
 - **AEGL-1: Headaches vs. Slight Dizziness**
 - **AEGL-2: Prenarcosis - Disabling... 'Ability to Escape'**
 - **Carcinogenicity**
 - Impact of Q_1 on toxicology-based AEGL values

Odor Detection - Hori

- **Studied "stench perception" of production & non-production workers in PVC plants**
 - 5-10 individuals from 15 plants studied for 'Stench Perception'
 - 50% of the non-production workers = ~200 ppm
 - 50% of the production workers = ~350 ppm
 - 'Minimum perceptive concentration' (a.k.a. Odor Detection)
 - 10 ppm for non-production workers
 - 20 ppm for production workers



Note: Odor Detection is good warning for AEGL-1 values established

Headache

Lester et al., 1963

• Study Design

- Exposed 6 subjects (3 men & 3 women) to 0, 4000, 8000, 12,000, 16,000 and 20,000 ppm
- Exposures were 5-minute duration
- Each adult was subjected to a different exposure sequence
- Minimum of 6 hours between two exposures

Headache

Lester et al., 1963

• Results

- 4000 ppm - No effect
- 8000 ppm - Subject 3 "slightly heady".... Others unaffected
 - (same subject slightly dizzy in room air)
- 12,000 ppm
 - Subject 2 unsure, somewhat dizzy in middle of exposure
 - Subject 6, reeling, swimming head, "just like getting gas"
 - Others unaffected
- 16,000 ppm (No effect by subject 5)
 - All others report various degrees of intoxication with dizziness, light headedness, some nausea, dulling of visual & auditory cues
 - these symptoms disappeared rapidly upon termination of the exposure
- 20,000 ppm - All subjects reported intoxicating effects. Subject 1 reporting a headache that persisted for 30 minutes. These symptoms appeared earlier in the exposure than at 16,000 ppm and the symptoms were more severe than at 16,000 ppm.

Headache

Lester et al., 1963

• Conclusions

- NOAEL is 8000 ppm
 - Subject 3 unaffected at 12,000 ppm (same subject slightly dizzy upon exposure to room air)
- LOAEL is 12,000 ppm but may be higher
- Effects observed are attributed to vinyl chloride because:
 - a dose-response is observed between 12,000 and 20,000 ppm
 - Subject 6 appeared to be more severely affected at 12,000 ppm than 16,000 ppm which may not be real
 - Effects disappeared rapidly following termination of exposure
- A headache that only lasts for 30 minutes is not typical & most likely, was due to vinyl chloride exposure.

Headache

Patty et al., 1930

• Results

- Exposed 2 individuals to 25,000 ppm for 3 minutes
 - Dizziness and slight disorientation
 - Slight headache noted which lasted for only 30 minutes.

Headache

Patty et al., 1930

• Conclusions

- Results are consistent with Lester
 - headache reported which lasted only 30 minutes

Headache

Baretta et al., 1969

• Study Design

- Exposed individuals to Vinyl Chloride
 - 50 ppm (6 individuals)
 - 250 ppm (4 individuals)
 - 500 ppm
 - 7 individuals for 3.5 hours
 - 4 individuals for 7 hours
- Exposures were 3.5 hours duration with 0.5 hr for lunch (no exposure) followed by another 3.5 hour duration exposure

Headache

Baretta et al., 1969

• Results

- No complaints or changes in neurological response
- 50 ppm - No effect
- 250 ppm - Slight odor detected for first 5 minutes
- 500 ppm - Slight odor detected for first 5 minutes
 - 2 of 7 reported headaches

Headache

Baretta et al., 1969

• Conclusions

- Only 2 individuals reported headaches
 - they most likely occurred near the end of the 7-hour exposure and not within the first 3.5 hours
- AEGL Committee assumed headaches reported were observed after 3.5 hours

Does the AEGL SOP allow the Committee to re-assign the headaches to 3.5 hours when the authors did NOT specifically state that the headache reports occurred at the lunch break?

Past AEGL practice in handling symptom reports has been:
even if the authors report a time sequence for symptoms during a specific exposure, the complete exposure time is used to define whatever AEGL level the data are used for.

Headache

Baretta et al., 1969

• Conclusions

- Body burden following the 2 exposures in this case would only be slightly less than what subjects would have experienced in a 7-hour continuous exposure
- Headaches reported for this particular exposure can only be attributed to the total exposure & not to a portion thereof without specific information to the contrary.

Summary available data

AEGL 3

AEGL 2

25,000 ppm	3 min - disoriented, dizzy
20,000 ppm	5 min - intoxicated, headache
16,000 ppm	5 min - dizzy, intoxicated, dull visual, dull auditory

AEGL 1

★ LOAEL	12,000 ppm	5 min - 1 somewhat dizzy, 1-reeling, swimming head
NOAEL	8,000 ppm	5 min - 'slightly heady'
NOAEL	500 ppm	3.5 hr or 7 hr - 2 of 7 developed mild headache, no neurological effects
	250 ppm	3.5 hr - slight odor detection (1st 5 min) - no effects
	50 ppm	3.5 hr - slight odor detection (1st 5 min) - no effects

Calculating AEGL-1 (NON-DISABLING)

- 10- and 30 minute values should use data from Lester using 12,000 ppm (allows for C¹ rather than C²)
- One-, four- and 8-hour values should use Baretta value (420 min)
 - values would be 2x higher
 - Note: One-hour could be calculated both ways and use the average value

Calculating AEGL-1

	10 min	30 min	60 min	4 hr	8 hr
Current AEGL	310	310	250	140	70
To be considered	2000	670	333 (Lester) 500 (Baretta) 415 average	280	140

Calculating AEGL-2 (DISABLING)

- AEGL-2 values based on NOAEL of 12,000 ppm (Baretta)
- Considerations:
 - Effects reported by Lester at 16,000 or 20,000 ppm do not appear to be truly disabling
 - Data suggests an even higher number than 20,000 ppm could be used
 - Consider study by Patty (25,000 ppm for 3 minutes)
- Proposed Basis: Using a minimum value of 20,000 ppm allowed the following AEGL-2 values to be calculated

Calculating AEGL-2 (DISABLING)

Recall: Flat-line

	10 min	30 min	60 min	4 hr	8 hr
Current AEGL	2800	1600	1200	820	820
To be considered	4710	2700	1925	1360	1360

Results

	10 min	30 min	60 min	4 hr	8 hr
AEGL-1					
Current AEGL	310	310	250	140	70
To be considered	2000	670	333 (Lester) 500 (Baretta) 415 average	280	140
AEGL-2					
Current AEGL	2800	1600	1200	820	820
To be considered	4710	2700	1925	1360	1360
AEGL-3					
Current	12,000	6800	4800	3400	3400

Calculation of AEGL-1

AEGL-1		
	Current	Proposed
	$C^t \times t = k$ for 30 & 60 minutes (10 min = 30 min) $C^t \times t = k$ for 4 and 8 hour	$C^t \times t = k$ for 10 and 30 minutes and 1, 4 and 8 hours
AEGL-1	$k = (491 \text{ ppm})^t \times 210 \text{ min} = 2.49 \times 10E+10 \text{ ppm}^t \text{ min}$ $k = (491 \text{ ppm})^t \times 210 \text{ min} = 103110 \text{ ppm min}$	$k = (12,000 \text{ ppm})^t \times 5 \text{ minutes} = 60,000 \text{ ppm min for 10, 30 and 60 minutes}$ $k = (491 \text{ ppm})^t \times 420 \text{ min} = 4.97 \times 10E+10 \text{ ppm min}$
10-min AEGL-1	$= 30 \text{ min AEGL-1}$ $= 310 \text{ ppm}$	$C \times 10 \text{ min}/3 = 60,000 \text{ ppm min}$ $C = 60,000 \text{ ppm min}/10 \text{ min} \times 3$ $C = 2000 \text{ ppm}$
30-min AEGL-1	$= C^t \times 30 \text{ min} = 2.49 \times 10E+10 \text{ ppm}^t \text{ min}$ $= 939.25$ $= 939 \text{ ppm}/3 = 310 \text{ ppm}$	$C \times 30 \text{ min}/3 = 60,000 \text{ ppm min}$ $C = 60,000 \text{ ppm min}/30 \text{ min} \times 3$ $C = 677 \text{ ppm}$
1-hour AEGL-1	$= C^t \times 60 = 2.49 \times 10E+10 \text{ ppm}^t \text{ min}$ $= 745$ $= 745 \text{ ppm}/3 = 250 \text{ ppm}$	$C \times 60 \text{ min}/3 = 60,000 \text{ ppm min}$ $C = 60,000 \text{ ppm min}/60 \text{ min} \times 3$ $C = 333 \text{ ppm}$ $C \times 60 \text{ min}/3 = 4.97 \times 10E+10 \text{ ppm min}$ $C = 4.97 \times 10E+10 \text{ ppm min}/60 \times 3$ $C = 500 \text{ ppm}$ Average = 415 ppm
4-hr AEGL-1	$C \times 240 \text{ min} = 103110 \text{ ppm min}$ $C = 430$ $= 430 \text{ ppm}/3 = 140 \text{ ppm}$	$C \times 240 \text{ min}/3 = 4.97 \times 10E+10 \text{ ppm min}$ $C = 4.97 \times 10E+10 \text{ ppm min}/240 \times 3$ $C = 280 \text{ ppm}$
8-hr AEGL-1	$C \times 480 \text{ min} = 103110 \text{ ppm min}$ $C = 214 \text{ ppm}$ $214 \text{ ppm}/3 = 70 \text{ ppm}$	$C \times 480 \text{ min}/3 = 4.97 \times 10E+10 \text{ ppm min}$ $C = 4.97 \times 10E+10 \text{ ppm min}/480 \times 3$ $C = 140 \text{ ppm}$

Calculation of AEGL-2

AEGL-2

	Current	Proposed
	$C^2 \times t = k$ for 10 and 30 minutes & 1 and 2 hours flatlining from 4 hr to 8 hr $k = (12,000 \text{ ppm})^2 \times 5 \text{ min} = 7.2 \times 10E+8 \text{ ppm}^2 \text{ min}$	$C^2 \times t = k$ for 10 and 30 minutes & 1 and 2 hours flatlining from 4 hr to 8 hr $k = (20,000 \text{ ppm})^2 \times 5 \text{ min} = 2.0 \times 10E+9 \text{ ppm}^2 \text{ min}$
10-min AEGL-2	$C^2 \times 10 \text{ min} = 7.2 \times 10E+8 \text{ ppm}^2 \text{ min}$ $C = 8485 \text{ ppm}$ $10 \text{ min AEGL-2} = 8485 \text{ ppm}/3$ $= 2800 \text{ ppm}$	$C^2 \times 10 \text{ min} = 2.0 \times 10E+9 \text{ ppm}^2 \text{ min}$ $C = 14142 \text{ ppm}$ $10 \text{ min AEGL-2} = 14142 \text{ ppm}/3$ $= 4710 \text{ ppm}$
30-min AEGL-2	$C^2 \times 30 \text{ min} = 7.2 \times 10E+8 \text{ ppm}^2 \text{ min}$ $C = 4899 \text{ ppm}$ $30 \text{ min AEGL-2} = 4899 \text{ ppm}/3$ $= 1600 \text{ ppm}$	$C^2 \times 30 \text{ min} = 2.0 \times 10E+9 \text{ ppm}^2 \text{ min}$ $C = 8165 \text{ ppm}$ $30 \text{ min AEGL-2} = 8165 \text{ ppm}/3$ $= 2700 \text{ ppm}$
1-hour AEGL-2	$C^2 \times 60 \text{ min} = 7.2 \times 10E+8 \text{ ppm}^2 \text{ min}$ $C = 3464 \text{ ppm}$ $1\text{-hour AEGL-2} = 3464 \text{ ppm}/3$ $= 1200 \text{ ppm}$	$C^2 \times 60 \text{ min} = 2.0 \times 10E+9 \text{ ppm}^2 \text{ min}$ $C = 5773 \text{ ppm}$ $1\text{-hour AEGL-2} = 5773 \text{ ppm}/3$ $= 1925 \text{ ppm}$
2 hr steady state	$C^2 \times 120 \text{ min} = 7.2 \times 10E+8 \text{ ppm}^2 \text{ min}$ $C = 2450 \text{ ppm}$ $2\text{-hour steady state} = 2450 \text{ ppm}/3$ $= 820 \text{ ppm}$	$C^2 \times 120 \text{ min} = 2.0 \times 10E+9 \text{ ppm}^2 \text{ min}$ $C = 4082 \text{ ppm}$ $2\text{-hour steady state} = 4082 \text{ ppm}/3$ $= 1360 \text{ ppm}$
4-hr AEGL-2	4-hour AEGL-2 = 2-hour steady state/3 $= 820 \text{ ppm}$	4-hour AEGL-2 = 2-hour steady state/3 $= 1360 \text{ ppm}$
8-hr AEGL-2	8-hour AEGL-2 = 4 hour AEGL-2 $= 820 \text{ ppm}$	8-hour AEGL-2 = 4 hour AEGL-2 $= 1360 \text{ ppm}$

Cancer Issue - Ward et al., 2000

- 12,700 Individual subjects in IARC study
- Started monitoring workforce in 1955
- Numbers of individuals are greater than 12,700 since workers hired <<1955 only satisfy higher criteria

Cancer Issue - Ward et al., 2000

Liver cancer incidence from all countries by cumulative exposure			
<u>Cumulative exposure</u> <u>(ppm.years)</u>	<u>Number of</u> <u>individuals</u>	<u>Incidence</u> <u>(observed/expected)</u>	<u>SMR</u>
unknown	2243	2/3.19	63
0-734	9552	11/10.26	107
735-2379	2772	9/3.32	271
2380-5188	1463	10/2.62	382
5189-7531	515	10/1.77	566
7532+	215	11/0.96	1140
Total	12700	53/22.11	240

Table 12 of Ward et al., (2000). Update of the follow-up of mortality and cancer incidence among European workers employed in the vinyl chloride industry. IARC Internal report #00/001

Note: Number of individuals cited for various employment intervals add up to >12,700 since individuals can meet more than one criteria Table D.7.

Cancer Issue - Ward et al., 2000

Liver cancer incidence from all countries			
<u>Duration of</u> <u>employment (years)</u>	<u>Number of</u> <u>individuals</u>	<u>Incidence</u> <u>(observed/expected)</u>	<u>SMR</u>
<3	10,961	1/1.61	62
3-6	8999	3/1.44	208
7-11	6919	7/1.35	517
12-18	4610	5/1.42	352
19+	2006	13/1.46	893
Total	12,700	29/7.29	398

Table T1.7 of Ward et al., (2000). Update of the follow-up of mortality and cancer incidence among European workers employed in the vinyl chloride industry. IARC Internal report #00/001

Note: Note: Number of individuals cited for various employment intervals add up to >12,700 since individuals can meet more than one criteria Table D.6.

Cancer Issue - Mundt et al., 1999

<u>Length of exposure (years)</u>	<u>Liver cancer incidence</u>		<u>SMR</u>
	<u>Number of individuals</u>	<u>Incidence (observed/expected)</u>	
1-4	4774	7/8.43	83
5-9	2383	10/4.65	215
10-19	1992	39/5.74	679
20+	960	24/3.49	688

Table 21 of Mundt et al., (1999). Epidemiological study of men employed in the vinyl chloride industry between 1942 and 1972: I) Reanalysis of mortality through December 31, 1982; and II) Update of mortality through December 31, 1995

Cancer Issue

● **Kielhorn et al., (2000) concluded:**

"Fortunately, it seems that ASL is correlated with only high exposures over long periods."

Cancer Issue - Conclusion

- **No increase in cancer risk based on:**
 - years worked (1-3 years [Ward] or 1-4 years [Mundt])
 - ppm-years (<734 ppm years [Ward])



Thus, it is highly unlikely that there would be an increased liver cancer incidence following a single exposure to vinyl chloride.

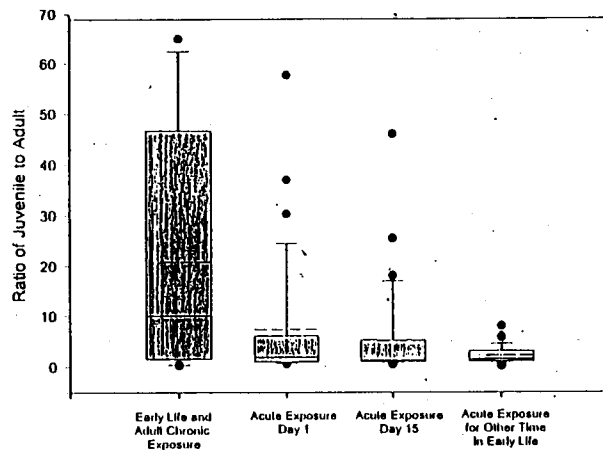


Figure 1: Ratio of juvenile to adult tumor incidence over time for carcinogens primarily acting through a mutagenic mode of action. The box represents the 25th to 75th percentile. The solid line is the median, the dashed line is the mean.

EPA, guidance early life exposure, DRAFT, Feb. 2003

Vinyl Chloride, Cancer Risk Calculations

TABLE C1: SUMMARY OF PROPOSED AEGL VALUES FOR VINYL CHLORIDE						
Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL-1 *) (Non-disabling)	450 ppm (1,200 mg/m ³)	310 ppm (800 mg/m ³)	250 ppm (650 mg/m ³)	140 ppm (360 mg/m ³)	70 ppm (180 mg/m ³)	mild headaches in 2/7 humans (Baretta et al., 1969)
AEGL-2 *) (Disabling)	2,800 ppm (7,300 mg/m ³)	1,600 ppm (4,100 mg/m ³)	1,200 ppm (3,100 mg/m ³)	820 ppm (2,100 mg/m ³)	820 ppm (2,100 mg/m ³)	mild dizziness in 1/6 humans (Lester et al., 1963)
AEGL-3 *) (Lethal)	12,000 ppm (31,000 mg/m ³)	6,800 ppm (18,000 mg/m ³)	4,800 ppm (12,000 mg/m ³)	3,400 ppm (8,800 mg/m ³)	3,400 ppm (8,800 mg/m ³)	cardiac sensitization (Clark and Tinston, 1982; 1973)

*) Derived AEGL- levels do not protect from DNA-adducts and may not protect from malignancies due to short term VC exposure

Estimations on carcinogenic potency after single exposure

- Calculation A:** unit risk for continuous lifetime exposure from EPA (2002), Transformation by default procedure to single exposure (SOP: i.e. linear transformation, correction by a factor of 6)
- Calculation B:** unit risk for childhood (possibly first 10 years of age) EPA (2002), Transformation by default procedure to single exposure (SOP: i.e. linear transformation, correction by a factor of 6)
- Calculation C:** five-weeks animal study from Maltoni et al. (1981), 5 weeks (animals) = 150 weeks (humans), linear transformation to a single exposure; identical to Froment et al. (1994)
- Calculation D:** DNA adducts after single exposure (adult animals) no increase of relevant adducts above background plus uncertainty factors

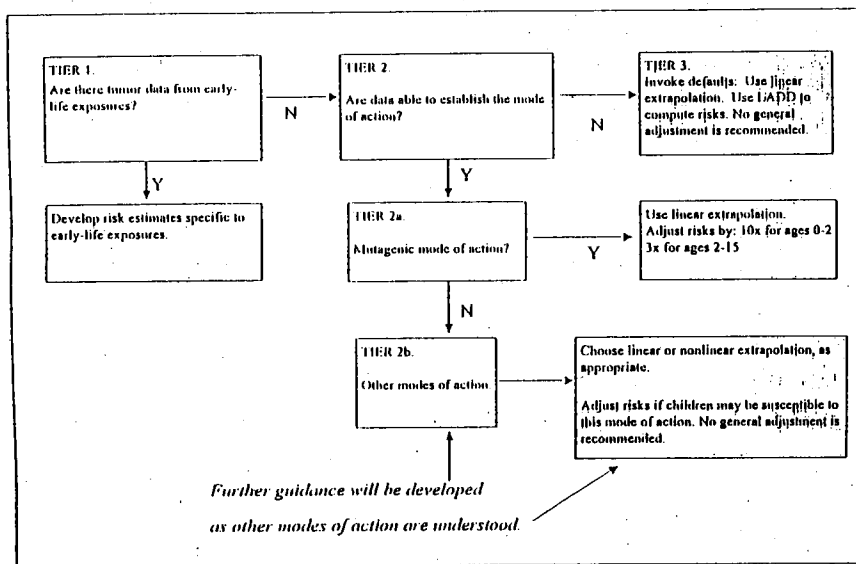


Figure 3: Risk assessment of early life exposure EPA, guidance early life exposure, DRAFT, Feb. 2003

Calculation B:

unit risk for childhood (possibly first 10 years of age) EPA (2002), Transformation by default procedure to single exposure (SOP: i.e. linear transformation, correction by a factor of 6)

unit risk childhood exp.: 4.4×10^{-6} per $\mu\text{g}/\text{m}^3$ (first 10 years)

1 : 10,000: $22.73 \mu\text{g}/\text{m}^3$

$22.73 \mu\text{g}/\text{m}^3 \times 3657 = 83.1 \text{ mg}/\text{m}^3$

$83.1 \text{ mg}/\text{m}^3 \times 1/6 = 13.85 \text{ mg}/\text{m}^3$

24-hour exposure = $13.85 \text{ mg}/\text{m}^3$ (5.35 ppm)

8-hour exposure = $41.6 \text{ mg}/\text{m}^3$ (16.1 ppm)

4-hour exposure = $83.1 \text{ mg}/\text{m}^3$ (32.1 ppm)

1-hour exposure = $332 \text{ mg}/\text{m}^3$ (128 ppm)

30-minute exposure = $665 \text{ mg}/\text{m}^3$ (257 ppm)

10-minute exposure > $1995 \text{ mg}/\text{m}^3$ (770 ppm)¹

¹ Because the metabolic pathway generating the intermediate believed to be responsible for the carcinogenic response becomes non-linear at an exposure >800 mg/m^3 , an external exposure in excess of that calculated is necessary to give 10^{-4} risk.

Calculation A

unit risk for continuous lifetime exposure from EPA (2002), Transformation by default procedure to single exposure (SOP: i.e. linear transformation, correction by a factor of 6)

unit risk: 8.8×10^{-6} per $\mu\text{g}/\text{m}^3$

dose at risk 1 : 10,000: $11.36 \mu\text{g}/\text{m}^3$

$11.36 \mu\text{g}/\text{m}^3 \times 25600 \text{ d} = 291 \text{ mg}/\text{m}^3$

$291 \text{ mg}/\text{m}^3 \times 1/6 = 48.5 \text{ mg}/\text{m}^3$

24-hour exposure = $49 \text{ mg}/\text{m}^3$ (19 ppm)

8-hour exposure = $146 \text{ mg}/\text{m}^3$ (56 ppm)

4-hour exposure = $291 \text{ mg}/\text{m}^3$ (112 ppm)

1-hour exposure > $1,164 \text{ mg}/\text{m}^3$ (449 ppm)¹

30-minute exposure > $2,328 \text{ mg}/\text{m}^3$ (899 ppm)¹

10-minute exposure > $7,056 \text{ mg}/\text{m}^3$ (2736 ppm)¹

¹ Because the metabolic pathway generating the intermediate believed to be responsible for the carcinogenic response becomes non-linear at an exposure >800 mg/m^3 , an external exposure in excess of that calculated is necessary to give 10^{-4} risk.

TABLE C3: CONVERSION OF ADMINISTERED VC DOSE TO A HUMAN EQUIVALENT CONCENTRATION (data from EPA, 2000a, b)

Admin. conc. (ppm) ^a	Metabolite (mg/L liver) ^b	HEC (ppm) ^c
0	0	0
1	0.59	0.2
5	2.96	1
10	5.9	2
25	14.61	4.6
50	31.27	10.1
100	55.95	19
150	76.67	26
200	90	31
250	103.45	35
500	116.94	40
2,500	134.37	48
6,000	143.72	51

^a Animals exposed 4 hours/day, 5 days/week for 52 weeks.

^b Dose metric (lifetime average delivered dose in female rats) calculated from PBPK modeling of the administered animal concentration.

^c Continuous human exposure concentration over a lifetime required to produce an equivalent mg metabolite/L of liver.

Calculation C:

five-weeks animal study from Maltoni et al. (1981), 5 weeks (animals) = 150 weeks (humans), linear transformation to a single exposure

Exposure concentration: $6,000 \text{ ppm}$
liver angiosarcoma 40.5 %

$6,000 \text{ ppm}$ (4h/d, 5d/w) rat 51 ppm (132 mg/m^3), Clewell et al. (1995)

$132 \text{ mg}/\text{m}^3 = 40.5\%$
 $\Rightarrow 3.3 \text{ mg}/\text{m}^3 = 1\%$
 $\Rightarrow 33 \mu\text{g}/\text{m}^3 = 0.01\% = 1:10,000$

dose at risk (1:10,000): $33.0 \mu\text{g}/\text{m}^3$

75 years (human): 2.5 years (rat) = 30 (5 weeks x 7 days x 30 relative time) = 1050

$33.0 \mu\text{g}/\text{m}^3 \times 1050 \text{ days} = 34.7 \text{ mg}/\text{m}^3$ (14 ppm)

24-hour exposure = $35 \text{ mg}/\text{m}^3$ (14 ppm)

8-hour exposure = $108 \text{ mg}/\text{m}^3$ (42 ppm)

4-hour exposure = $217 \text{ mg}/\text{m}^3$ (84 ppm)

1-hour exposure > $866 \text{ mg}/\text{m}^3$ (334 ppm)

30-minute exposure > $1733 \text{ mg}/\text{m}^3$ (669 ppm)

10-minute exposure > $5199 \text{ mg}/\text{m}^3$ (2007 ppm)

¹ Because the metabolic pathway generating the intermediate believed to be responsible for the carcinogenic response becomes non-linear at an exposure >800 mg/m^3 , an external exposure in excess of that calculated is necessary to give 10^{-4} risk.

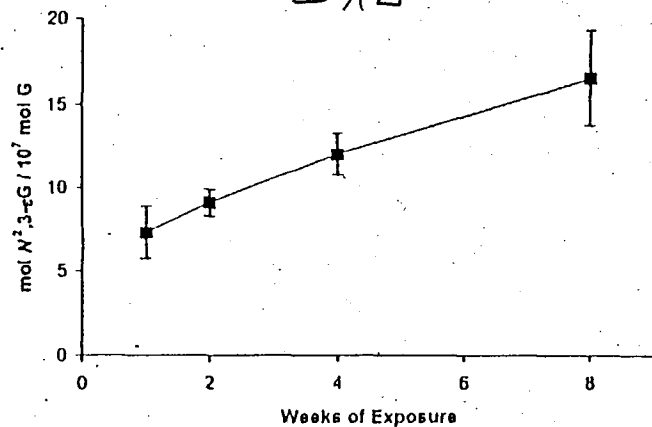
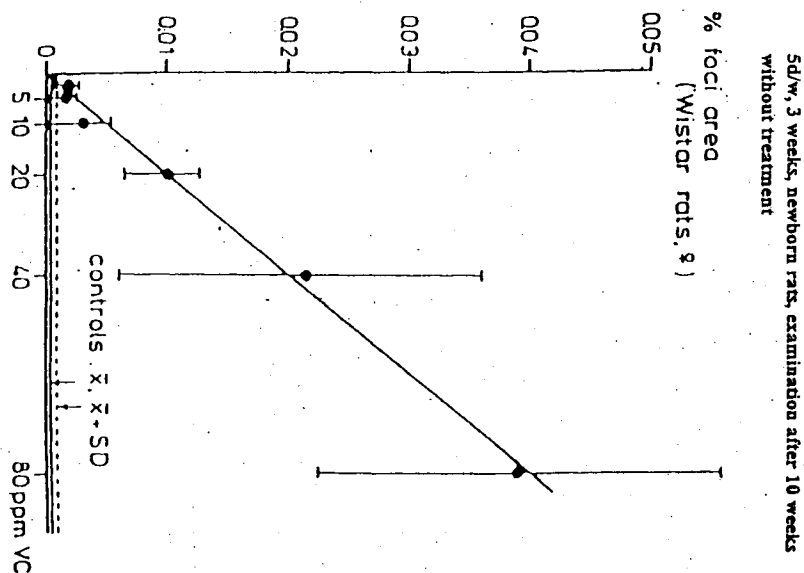


Fig. 5: Accumulation of N₂,3-εG in whole liver DNA from rats exposed to 500 ppm VC for the indicated times (4 h/day, 5 days/week). The rats were killed immediately after the exposures. The results from 5 rats/group are shown as the mean ± SE.

Source: Morinello et al., 2002



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Calculation B:
DNA adducts after single exposure (adult animals) no increase of relevant adducts above background plus uncertainty factors

1. ethenobases were shown to possess miscoding properties (Barbin, 2000)
2. ethenobases generate mainly base pair substitution mutations (Barbin, 2000)
3. ethenobases assumed to be initiating lesions in carcinogenesis (Barbin, 2000)
4. high correlation between DNA-adducts formation (εG) and incidence of haemangiosarcoma in mice after exposure to vinyl fluoride (Svenberg et al., 1999)

Single exposure to 45 ppm VC (6 hours)

no increase of relevant cyclic adducts (εA, εC, εG) in adult rats (estimated from results from Watson et al., 1991)

- 10 -

Svenberg et al., 1999 (OEG) 600 ppm 5d, 4h/d, rat	Svenberg et al., 1999 (εG) 600 ppm 5d, 4h/d, rat	Ciroussel et al., 1990 (εdAdo/dAdo) 500 ppm 2 weeks, 7h/d, rat	Ciroussel et al., 1990 (εdCyd/dCyd) 500 ppm 2 weeks, 7h/d, rat
162/43=3.8	1.81/0.47=3.9	1.3/0.19=6.8	4.92/0.8=6.15

Morinello et al., 2002a (εG) 10 ppm 5d, 6h/d, SD-rat (HEP)	Morinello et al., 2002a (εG) 1100 ppm: 5d, 6h/d, SD-rat (HEP)		
4.1/1.4=2.9	9.7/5.5=1.8		

DNA-ADDUCTS AFTER SHORT TERM EXPOSURE TO VC

- Adult rats, 250 ppm, single exposure, 5 hours: 23 pmol/ 100 mg liver wet weight, 0.35 pmol d-guanosine alkylation product (Bolt et al., 1980)
- Adult rats, 45 ppm, single exposure, 6 hours (Watson et al., 1991):

VC-inhalation (ppm)	0	1	10	45	100	600
7-(2'-oxoethyl)guanine (OEG) [adducts/nucleotides]		0.026/10 ⁶	0.28/10 ⁶	1.28/10 ⁶		
1,N ⁶ -ethenoadenine (εA)				<1/10 ⁴		
3,N ⁶ -ethenocytosine (εC)				<1/10 ⁴		
N ² ,3-ethenoguanine (εG)*				≈ 1/10 ⁴		
<i>for comparison (Svenberg et al., 1999):</i>						
εG- Background (rat)	0.9/10 ⁷					
εG, 5 days			2/10 ⁷		6.8/10 ⁷	
εG, 20 days			5.3/10 ⁷		2.3/10 ⁶	
εG, 4h/d, 5d, immed. after exposure						3.8/10 ⁶
εG, 4h/d, 5d, 14 days after exposure						4.7/10 ⁷
εG- Background (human)	6/10 ⁴ - 7/10 ⁷					

* estimated (εG) from ratio = 1/100 OEG/εG in other VC experiments

Source: Isaacs, J. T., Cancer Research, Vol. 45, 1985, pp. 4827-4832

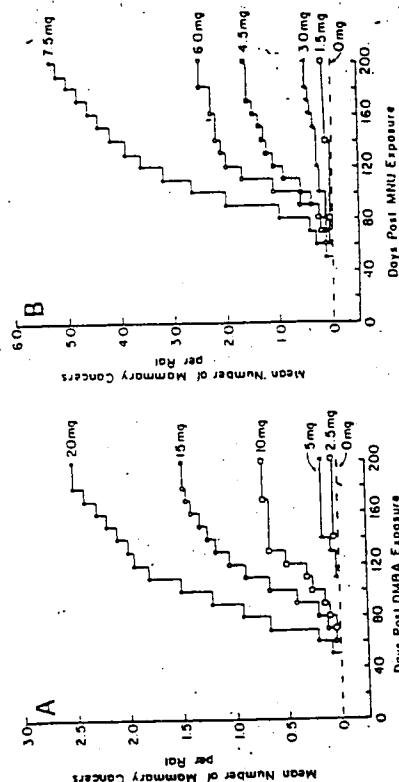


Chart 1. Temporal pattern of mammary cancer appearance following a single exposure to various doses of DMBA (A) or MNU (B).

low risk guidance level (LRGL)

Key study: Watson et al., 1991; Svenberg et al., 1999; Barbin, 2000

Toxicity endpoint: DNA-adducts; background adduct levels at single 45 ppm exposure of rats is taken as LRGL-NOAEL (6 hours)

Uncertainty/modifying factors: Combined uncertainty factor of 10
1 for interspecies variability
10 for intraspecies variability

Time Scaling: $C^3 \times t = k$ for extrapolation to 4-hour, 1-hour, and 30-minute;
 $k = (45 \text{ ppm})^3 \times 360 \text{ min} = 3.2 \times 10^6 \text{ ppm}^3 \text{ min}$
 $C^1 \times t = k$ for extrapolation to 8-hours;
 $k = 45 \text{ ppm} \times 360 \text{ min} = 16,200 \text{ ppm}^1 \text{ min}$
10-minute LRGL = 30-minute LRGL

10-minute LRGL = 30-min LRGL = 10 ppm (= 26 mg/m³)

30-minute LRGL $C^3 \times 30 \text{ min} = 3.2 \times 10^6 \text{ ppm}^3 \text{ min}$
 $C = 103 \text{ ppm}$
30-min LRGL = 103 ppm/10 = 10 ppm (= 26 mg/m³)

1-hour LRGL $C^3 \times 60 \text{ min} = 3.2 \times 10^6 \text{ ppm}^3 \text{ min}$
 $C = 81.8 \text{ ppm}$
1-h LRGL = 81.8 ppm/10 = 8.2 ppm (= 21 mg/m³)

4-hour LRGL $C^3 \times 240 \text{ min} = 3.2 \times 10^6 \text{ ppm}^3 \text{ min}$
 $C = 51.5 \text{ ppm}$
4-h LRGL = 51.5 ppm/10 = 5.1 ppm (= 13 mg/m³)

8-hour LRGL $C \times 480 \text{ min} = 16200 \text{ ppm}^1 \text{ min}$
 $C = 33.75 \text{ ppm}$
8-h LRGL = 34 ppm/10 = 3.4 ppm (= 8.8 mg/m³)

Table C7: Comparison of AEGL values (VC) based on nonmalignant effects and different estimations of carcinogenic risk after single exposure					
[ppm]	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1 (Baretta et al., UF:3; n=3,1)	450	310	250	140	70
AEGL-2 (Lester et al., UF:3; n=2 to 2h; 2h=4h=8h)	2,800	1,600	1,200	820	820
AEGL-3 (Clark & Tinston; UF:3; n=2 to 2h; 2h=4h=8h)	12,000	6,800	4,800	3,400	3,400
concentrations assumed to correspond to carcinogenic risk 1:10,000 or threshold (calculation D):					
CALCULATION A (unit risk) default SOP;	>2700	>900	>450	110	56
CALCULATION B (unit risk children)	>770	260	130	32	16
CALCULATION C (Maltoni et al., 1981)	>2000	>670	>330	84	42
CALCULATION D (Watson et al., (DNA))	10	10	8.2	5.1	3.4

ACUTE EXPOSURE GUIDELINE LEVELS for HYDROGEN BROMIDE

National Advisory Committee for AEGLs Meeting 27
March 7-8, 2003

ORNL Staff Scientist:
Sylvia S. Talmage

Chemical Manager:
Larry Gephart

Chemical Reviewers:
John Hinz
Nancy Kim

HYDROGEN BROMIDE

Human Toxicity Data
Single study, reported in ACGIH (2002)

Human Responses to Hydrogen Bromide Vapor					
Response	2 ppm	3 ppm	4 ppm	5 ppm	6 ppm
Detectable odor	6	6	6	6	6
Nose irritation	0	1	3	6	6
Throat irritation	0	1	1	1	1
Eye irritation	0	0	0	0	0

0 indicates no subjective irritation in any subject.
Numbers other than 0 indicate number of subjects responding (out of six); responses range from slight, stinging sensation to a definite feeling of irritation.

AEGL-1:
3 ppm is the threshold for irritation (NOAEL for notable discomfort)
Divide by an intraspecies uncertainty factor of 3
Adaptation occurs to slight irritation; use 1 ppm across all exposure durations

HYDROGEN BROMIDE

Animal Toxicity Data

Non-lethal concentrations: 100-1000 ppm for 30 minutes
HF, HCl, and HBr are similarly well scrubbed in the nasal passages of the rat with damage to the respiratory tract in the order: HF>HCl>HBr (Kusewitt et al. 1989; Stavert et al. 1991)

Lethality: HBr is ~ "half" as toxic as HF and similar in toxicity to HCl
1-hour LC₅₀ values: order of toxicity: HF>HBr>HCl

Relative Toxicities [1-Hour LC ₅₀ Values (ppm)] of HF, HCl, and HBr				
Species	HF	HCl	HBr	References
Rat	1278	3124	2858	MacEwen and Vernot 1972;
Mouse	501	1108	814	MacEwen and Vernot 1974; Vernot et al. 1977

HYDROGEN BROMIDE

AEGL-2:
No human or animal data relevant to development of AEGL-2
Use structure-activity relationship for non-lethality: HF>HCl>HBr
AEGLs for HF and HCl have reached Interim status/accepted by the NAS

Use approved values for the more toxic HF:
10-minute no-effect concentration of 950 ppm (Dalbey 1996)
243 ppm for 1 hour: irritation in dogs (Rosenholtz et al. 1963)
Total UF of 10; time scaled with n = 2

Because all three hydrogen halides are well scrubbed and human data for HF and HCl were inconsistent with the time-scaled 8-hour values, set the 8-hour value equal to the 4-hour value

Proposed AEGL-2 Values

10 minutes	30 minutes	1 hour	4 hours	8 hours
95 ppm	34 ppm	24 ppm	12 ppm	12 ppm

HYDROGEN BROMIDE

AEGL-3:

Use lethality data:

1-hour LC_{50} (rat) = 2858 ppm (MacEwen and Vernot 1972)

1-hour, 10% mortality (rat) = 2205 ppm

1-hour LC_{01} (rat) = 1350 ppm

30 minutes, 8% mortality (rat) = 1300 ppm (Stavert et al. 1991)

30 minutes, no deaths (rat) = 1000 ppm

Divide 30-minute 1000 ppm NOAEL for lethality by combined UF of 10

Time scaled with $n = 2$

Because all three hydrogen halides are well scrubbed and human data for

HF and HCl were inconsistent with the time-scaled 8-hour values, set the 8-hour value equal to the 4-hour value

Use benchmark dose approach with data of MacEwen and Vernot (1972)

Proposed AEGL-3 Values

	10 minutes	30 minutes	1 hour	4 hours	8 hours
NOAEL	170 ppm	100 ppm	70 ppm	35 ppm	35 ppm
$BMCL_{01}$	218 ppm	126 ppm	89 ppm	45 ppm	32 ppm

HYDROGEN HALIDE AEGLs

Classification	Exposure Duration (Values in ppm)				
	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1					
HF	1	1	1	1	1
HBr	1	1	1	1	1
HCl	1.8	1.8	1.8	1.8	1.8
AEGL-2					
HF	95	34	24	12	12
HBr	95	34	24	12	12
HCl	100	43	22	11	11
AEGL-3					
HF	170	62	44	22	22
HBr	170	100	70	35	35
	218	126	89	45	32
HCl	620	210	100	26	26

Chemical, Physical, and Toxic Properties of the Hydrogen Halides

Property	Hydrogen fluoride	Hydrogen chloride	Hydrogen bromide
Molecular weight	20	36.5	81
Water solubility	infinite	67 g/100 g	freely
Capacity to be scrubbed	similar ($HF \geq HCl \geq HBr$)		
LC_{50} values*			
1-hour - rat	1278, 1395	3124	2858
1-hour - mouse	501, 342	1108	814
RD_{50}	151 ppm	309 ppm	not available

* MacEwen and Vernot 1972; 1974, Vernot et al. 1977, Wohlschlager et al. 1976.

TITANIUM TETRACHLORIDE (TiCl₄)

- ◆ Colorless liquid that fumes when in contact moist air
- ◆ TiCl₄ has high affinity for water and is readily hydrolyzed by water, producing titanium oxychlorides, hydrochloric acid, and heat
- ◆ Used to manufacture TiO₂ pigments, titanium metal, artificial pearls, iridescent glass, and military smoke screen
- ◆ Produced from chlorination of titanium dioxide at high temperatures in presence of reducing agent; main producers of TiCl₄ are producers of TiO₂
- ◆ Estimated world-wide production of 6 million tons in 1996
- ◆ Penetrating, acrid, and irritating odor; no reported odor threshold

◆ **Effects of exposure**

- ▶ Contact with liquid causes deep, severe burns; exposure to fumes may result in burns
- ▶ Acute exposure:
Humans: cough, chest tightness, eye irritation/corneal damage, acute respiratory distress from pneumonitis/ pulmonary findings similar to thermal respiratory injury

Animals: death from pulmonary edema; signs of eye closing and gasping, corneal opacity, lung congestion/respiratory distress
- ▶ Studies have reported that TiCl₄ is much more toxic than what would be predicted from the molar equivalents of HCl (16-times more toxic than what is predicted)

Kelly, 1980

- ▶ Groups of 6 male rats exposed to various conc. for 2, 5, 15, 30, 60, 120, or 240 min. by head-only inhalation exposures to determine LC₅₀ values
- ▶ Results:

duration (min)	LC ₅₀ value (ppm)
2	13,940
5	4600
15	713
30	390
60	171
120	143
240	59
- ▶ Clinical signs: eye closing and gasping during exposure; corneal opacity, weight loss and lung congestion after exposure
- ▶ Histopathology revealed inflamed airways, hypermucous secretion, epithelial denudation, severe necrotic laryngitis, pulmonary congestion, and hemorrhage. Subsequent study demonstrated lesions are reversible.

Kelly, 1979

- ▶ Groups of 25 male rats exposed to 0.7, 1.3, or 6.5 ppm for 6 h/d, 5 d/wk for 4 wk
- ▶ 0.7 ppm No clinical signs or clinical chemistry changes; ↑ lung:bw ratio (126% of controls); pulmonary histopathology: mild dust-cell reaction
- ▶ 1.3 ppm No clinical signs; reversible urinalysis changes (↑ urine pH; ↓ urine osmolality); ↑ lung:bw ratio terminal kill and 2 wks post exposure (136 and 114% of controls); histopathology changes of acute inflammation of respiratory tract
- ▶ 6.5 ppm Clinical signs of labored breathing and ↓ bw gain (93% of controls); 2 rats died (test day 15; 23) from pulmonary damage; reversible urinalysis changes (↑ urine pH; ↓ urine osmolality); ↑ lung:bw ratio terminal kill and 2 wks post exposure (178 and 128% of controls); histopathology changes of acute inflammation of respiratory tract

Time scaling:

◆ Empirical derivation of n based on data from Kelly, 1980

- ▶ rat 2-, 5-, 15-, 30-, 60-, 120-, and 240-minute LC_{50} values of 13940, 4600, 713, 390, 171, 143, and 59 ppm, respectively
- ▶ $n = 0.88$

AEGL-1 Derivation

Key study: Kelly, 1979

Effects:

0.7 ppm for 6 hr - no acute effects, but provides general baseline of exposure conc. at which no one should experience notable discomfort, irritation, or certain asymptomatic, non-sensory effects.

Uncertainty factors: 10

- ▶ Interspecies UF: 3
 - ▶ Intraspecies UF: 3
- Total UF of 100 normally applied; endpoint below that defined for AEGL-1 and multiple exp. study

Time scaling: Derived value of $n=0.88$. The 10-min value set equal to 30-min value (6 h to 10 min). Could also set 6-hour value equal across time.

AEGL-1 Values for TiCl ₄ (ppm)				
10-min	30-min	1-hr	4-hr	8-hr
1.2	1.2	0.54	0.11	0.050
0.07	0.07	0.07	0.07	0.07

AEGL-2 Derivation

Key study: Kelly, 1979

Effects:

1.3 ppm for 6 hr - no clinical signs, but next exposure level approaches lethality threshold

Uncertainty factors: 10

- ▶ Interspecies UF: 3
 - ▶ Intraspecies UF: 3
- Total UF of 100 normally applied; endpoint below that defined for AEGL-1 and multiple exp. study

Time scaling: Derived value of $n=0.88$. The 10-min value set equal to 30-min value (6 h to 10 min). Could also set 6-hour value equal across time.

AEGL-2 Values for TiCl ₄ (ppm)				
10-min	30-min	1-hr	4-hr	8-hr
2.2	2.2	1.0	0.21	0.094
0.13	0.13	0.13	0.13	0.13

AEGL-3 Derivation

Key study:

Kelly, 1980

Effects: One-third calculated LC₅₀ values:

duration (min)	1/3 LC ₅₀ value (ppm)
15	240
30	130
60	57
120	48
240	20

Uncertainty factors: 10

- Interspecies UF: 3:
- Intraspecies UF: 3

Total UF of 100 normally applied. If one applies total UF of 100 or 30, 4-h AEGL-3 values are 0.20 or 0.67 ppm, respectively. A study reported rats exposed to 1.3 ppm TiCl₄ for 6 h/d, 5 d/wk for 24 months exhibited no clinical signs or differences in morbidity or mortality compared to controls (Lee et al., 1986). The 4-h AEGL-3 values using total UF of 100 or 30 are not consistent with available data.

Time scaling:

The adjusted, empirical values for the 30-, 60-, and 240-min exposure durations used for the respective AEGL timepoints. Using an n=0.88, the adjusted, 15-minute LC₅₀ value was used to extrapolate to 10 min, while the adjusted 240-minute LC₅₀ value was used to extrapolate to 480 min

AEGL-3 Values for TiCl ₄ (ppm)				
10-min	30-min	1-hr	4-hr	8-hr
38	13	5.7	2.0	0.91

Summary of AEGL Values for TiCl ₄ (ppm)					
Level	10-min	30-min	1-hr	4-hr	8-hr
AEGL-1	1.2	1.2	0.54	0.11	0.050
If flatline	0.07	0.07	0.07	0.07	0.07
AEGL-2	2.2	2.2	1.0	0.21	0.094
If flatline	0.13	0.13	0.13	0.13	0.13
AEGL-3	38	13	5.7	2.0	0.91

AEGL Values for Hydrogen Chloride (ppm)[value divided by 16]					
Level	10-min	30-min	1-hr	4-hr	8-hr
AEGL-1 ^a	1.8 [0.11]	1.8 [0.11]	1.8 [0.11]	1.8 [0.11]	1.8 [0.11]
AEGL-2 ^b	100 [6.3]	43 [2.7]	22 [1.4]	11 [0.69]	11 [0.69]
AEGL-3 ^c	620 [39]	210 [13]	100 [6.3]	26 [1.6]	26 [1.6]

^a No-adverse-effect-level in exercising human asthmatics

^b Mouse RD₅₀; Histopathology in rats

^c Estimated NOEL for death: 1-hr rat LC₅₀

Appendix A

National Advisory Committee (NAC) for Acute Exposure Guideline Levels (AEGLs) for Hazardous Substances

December 9-11, 2002

Final Meeting-27 Highlights

Bureau of Labor Statistics, U.S. Department of Labor
Postal Square Building, G-440, Rm. 7-8
2 Massachusetts Avenue, N.E., Washington D.C. 20212

INTRODUCTION

George Rusch, NAC/AEGL Chair, opened the meeting with brief remarks including appreciation to Surender Ahir, OSHA representative, for his excellent efforts in making arrangements for the NAC/AEGL-27 meeting. He also briefly noted the absence of Roger Garrett, AEGL Program Director, due to illness.

George Rusch made remarks on the productive working history with John Henshaw, Assistant Secretary, OSHA/DOL, who is involved in the Emergency Response Planning Committee. Today, John was regrettably not able to be here and Davis Layne, Deputy Assistant Secretary, OSHA/DOL, welcomed the NAC/AEGL Committee. Davis Layne stated that OSHA mostly utilizes data from chronic studies; there are a few OSHA regulations that utilize acute toxicity data as well. For example, OSHA uses IDLH values under its confined space regulation and acute toxicity data to classify various hazardous substances under the Hazard Communication Standard. OSHA appreciates any guidance given to the workers based on scientifically sound principles.

The draft NAC/AEGL-26 meeting highlights were reviewed with one minor change to update the current affiliation of Pam Dalton. A motion was made by Mark McClanahan and seconded by George Rodgers to accept the meeting highlights as presented with the aforementioned revision. The motion passed unanimously by a voice vote. The final version of the NAC/AEGL-26 meeting highlights are attached (Appendix A) and was distributed to the NAC/AEGL by e-mail on December 26, 2002.

The highlights of the NAC/AEGL-27 meeting are summarized below along with the Meeting Agenda (Attachment 1) and the Attendee List (Attachment 2). The subject categories of the highlights do not necessarily follow the order listed in the NAC/AEGL-27 Agenda.

STATUS REPORTS

NRC/COT Publication

Ernie Falke reported that AEGL Volume 2 was published in October 2002; complementary copies were mailed to all NAC/AEGL members. Volume 3 which includes Nerve agents (GA, GB, GD, GF, and VX), Sulfur mustard, Diborane, and Methyl isocyanate is at the stage of COT external review. It is expected to be published by early spring of 2003. Upon complete analyses of the COT 8th Interim Report, we may have another publication.

Critical Health Effects Starting Points for AEGL Determination: LOAEL vs NOAEL

George Rusch solicited comments from the Committee with respect to the Summary of Category V Chemicals distributed by Po-Yung Lu prior to the meeting (Attachment 3). The NAC/AEGL accepted the Summary except George Alexeeff who had a concern on the justification of Iron pentacarbonyl. It was decided that George Rusch will look into the issue further and resolve the concern. If necessary, this chemical will be revisited at a future NAC/AEGL meeting.

TECHNICAL ISSUE DISCUSSIONS

LOA Subcommittee Report **Mark McClanahan and Marc Ruijten**

The AEGL Odor Subcommittee held two conference calls prior to the December NAC/AEGL-27 meeting. The first conference call (November 7, 2002) discussed the use of the Level of Distinct Odor Awareness (LOA). The following summarizes the recommendations (Attachment 4) from the subcommittee:

All AEGLs should be health-based. Odor, even as defined by the LOA, will not serve as a surrogate for health-based values without health-based data. The level of distinct odor awareness will not substitute for health-based values. Include the LOA in the TSD as information supplementary to health-based AEGL values. A single value of the LOA should be presented in both the executive summary and the TSD. The authors should write the **LOA as, "Level of Distinct Odor Awareness,"** and not as "Level of Significant Odor Awareness." The "Level of Distinct Odor Awareness" reported in the TSD will be based on the odor threshold (TD₅₀), where 50% of the odor panel detects the odor and 50% does not and has the odor intensity of 3 (Distinct Odor). The inclusion of the LOA within the TSD does not preclude the use of odor descriptors such as fruity, fishy, nutty, pungent, etc., where appropriate within the TSD. A population-based array of the LOA will be presented in the Appendix. When a useful relationship to Hedonic Tone becomes available this characteristic should also be incorporated in the definition of the LOA reported in the TSD. A chemical-specific development of the LOA

should be placed in a TSD Appendix. A version of “Guidance for the Application of Odor in Chemical Emergencies,” should be incorporated into the SOP. At the December NAC/AEGL-27 meeting, the consensus of the members was to stop reporting odor data in Table 1. “Chemical and Physical Data” of the TSD.

The second conference call (December 4, 2002) discussed the use of LOAEL and NOAEL for definition of AEGL levels (Attachment 4).

The TSD documents should be as consistent as possible in selection of the sign or symptom chosen to define a specific AEGL level. The TSD should present a thorough justification of the sign/symptom chosen for a specific AEGL level. For AEGL-1, how do we resolve the discrepancy between the dictionary definition of the words notable and mild ? George Alexeef’s recent publication reported (36 chemicals) the LOAEL-to-NOAEL ratio to be: 2 at the 50th, 5 at the 90th, and 6.3 at the 95th percentile, respectively. George Alexeef has a database listing the signs and symptoms used to define AEGL levels obtained from completed NAS/AEGL documents. George will present this listing with some analysis at a future AEGL meeting. In some places, AEGL-1 concentrations have been proposed and used as re-entry levels for releases for which evacuations or traffic stoppages have occurred. When he is able to obtain the documentation, Tom Hornshaw will report on some estimated costs incurred when expressway traffic was halted because of a chemical release.

Application of Ratios for Determination of AEGLs

Tom Hornshaw

Tom Hornshaw presented a further analysis of the ratios between the AEGL-3 to AEGL-2 and AEGL-2 to AEGL-1 values for all five time periods (originally presented in September 2002, and summarized in the Meeting 26 highlights) (Attachment 5). As a result of actions taken at the September meeting, he updated his database to add values for two new chemicals, carbon disulfide and vinyl chloride, and changed values for two original chemicals, hydrogen sulfide and perchloromethyl mercaptan. These updates resulted in minor changes in the statistics for the AEGL-3-to-AEGL-2 ratios, with the mean, median, and 95th percentiles being all marginally smaller. In contrast, the updates to the data sets for AEGL-2-to-AEGL-1 ratios resulted in major changes, since the new AEGL-1 values for hydrogen sulfide changed these ratios from being extreme to “normal” outliers and the new AEGLs for carbon disulfide introduced an additional set of outliers. The changes include: the ratio means now have a range of 8.97–10.92 instead of 12.3–25.5; the medians have a range of 3.32–4.63 instead of 3.19–4.13; and the 95th percentiles have a range of 38.6–56.2 instead of 27.1–113.6.

Tom’s review of the toxicological data for the four outliers in the original analysis revealed that in all cases the higher-level AEGL was derived from animal data and the lower-level AEGL from human data, and the human endpoints were all neuropsychological and/or subjective in nature (headache, nausea, irritation, odor, etc.). He suggested that this implied that for certain chemicals

there will be effects in humans that will not be predictable from the animal toxicity database. The new AEGLs for carbon disulfide shed some additional light on this suggestion. This chemical differs from the other four outliers in that both the AEGL-2 and AEGL-1 values are derived from human data, with the AEGL-2 values protecting against acute neurotoxic effects and severe irritation and the AEGL-1 values protecting against the “antabuse syndrome” caused by genetically low activity of aldehyde dehydrogenase. In this case, the Committee has specifically accommodated an endpoint in humans that is not able to be addressed by animal studies in developing the AEGL-1 values. This adds another cautionary note regarding extrapolating from a higher-level AEGL to derive a lower. Tom continues to suggest that if the Committee wishes to be protective of these types of human endpoints, a default extrapolation divisor greater than the value of 3 used in the past is indicated in most cases.

In an effort to further shed light on this issue, Tom reviewed the data for those chemicals for which the NAC/AEGL has already derived AEGL-2 values from AEGL-3 values, methyl hydrazine, methacrylonitrile, iron pentacarbonyl, dimethylformamide, and epichlorohydrin. He also reviewed three additional chemicals that provided helpful information, phosphine (which has a steep dose/response curve for lethality), and nickel carbonyl and propionitrile (which are closely related to iron pentacarbonyl and methacrylonitrile, respectively). This resulted in some further insights into the issue of when to extrapolate and how large the divisor should be. From this review, Tom found that the steepness of the dose/response curve for lethality, toxicity data for a closely related chemical (if available), and the presence or absence of irritation and/or neuropsychological effects in the human record for a chemical, are key factors to help decide whether to extrapolate from a higher-level AEGL, and what should be the appropriate divisor. He concluded his presentation with a few suggestions:

- A default divisor of 3 to derive AEGL-2 values from AEGL-3 values is only appropriate when there is a very steep dose/response curve for lethality; i.e., one in which the difference between nonlethal and 100% lethal doses is in the range of a doubling of the dose.
- Where toxicity data consistent with AEGL-2 type effects are available for a chemical closely related to a chemical for which AEGL-2 type data are poor or lacking, the data for the closely related chemical should be considered in determining the divisor for extrapolating to AEGL-2 values.
- For chemicals for which data consistent with AEGL-2 type effects are poor or lacking, that do not have very steep dose/response curves, and that do not have closely related chemicals to help in determining an appropriate divisor for extrapolating from AEGL-3 values, the choice of such a divisor should be made carefully, if at all. Factors that should be reviewed in making this choice include: the steepness of the lethality dose/response curve, with steeper curves favoring extrapolation and shallower curves suggesting extrapolation may not adequately protect against all AEGL-2 type effects; the presence, with relevant exposure information, or absence of AEGL-1 type effects in the toxicity data base, which can help guide the selection of an appropriate divisor if present and cautions against extrapolation if absent; and the presence, with or without relevant

exposure information, of effects in humans such as neuropsychological effects that are not readily predictable from animal studies, which strongly suggest that if extrapolation is desired that the divisor be relatively large and in keeping with the severity of the effects reported. If the database for a chemical lacks these factors or the factors argue caution in the choice of whether to extrapolate, then a default divisor should be at least 19.

- Since relatively large changes in the statistics for the AEGL-2-to-AEGL-1 ratios occurred when new data for hydrogen sulfide and carbon disulfide were added, it appears that the overall predictive power of this data set is not yet acceptable to determine an appropriate default divisor for extrapolating from AEGL-2 values to AEGL-1 values. There is also no basis for extrapolation from AEGL-3 values to AEGL-1 values.
- Based on reviews of the databases for iron pentacarbonyl, methacrylonitrile, and dimethylformamide, these chemicals should be reviewed by the Committee to determine if the values derived for these chemicals are still thought to be protective for all AEGL-2 type effects.

Application of AEGL Values in Emergency Responses

Bob Snyder and Brian Buckly

Bob Snyder and associates from the Environmental and Occupational Health Science Institute, Rutgers University, summarized some of the work they are doing in establishing a procedure for emergency response to the release of chemicals or biologicals in a community. The key to the project is the measurement of air levels of chemicals in various areas of the community evaluated with respect to the AEGL values for the chemical at any time. Using the ten Berge modification of Haber's rule they have plotted AEGL values as continuous lines over time and demonstrated that although the committee decides on AEGL values at 5 specific time points, an equation can be written starting with those points which defines a line made up of many points each of which defines an AEGL at that time. It can be shown that during a release concentrations of the chemical may approach and exceed the AEGL levels for that chemical suggesting a toxic response to the chemical at the location studied. Equations were derived to predict when specific AEGL values will be achieved at any location. In these studies the value of K, as in $C \times T = K$, can be calculated and can be interpreted as a numerical expression of a response under the conditions of the experiment. These studies are still at an early stage and more detail will be presented as the data develop.

Acute Toxicity Threshold for Land Use Planning

Annick Pichard

Annick Pichard presented the overview of ACUTEX (Attachment 6). ACUTEX is a research project approved by the European Commission, started in December for a duration of three years. The objective of ACUTEX is to develop a methodology, a soft ware tool, and a Technical Guidance Document for establishing European Acute Exposure Threshold Levels (EU AETLs) for acute exposure scenarios. ACUTEX's aims toward:

1. Establishing a methodology, a software tool, and a Technical Guidance Document (TGD)
2. Developing EU AETLs for several chemicals as case studies according to the above TGD
3. Validating and improving the methodology by relevant case studies with end users and stakeholders.

EU AETLs have a great influence on the determination of the zone for land use and emergency planning. Threshold levels for acute exposures have been defined as concentrations in the air after accidental release which will cause different degrees of health impairment to human subjects exposed to the air. Air concentrations may reach to levels defined as levels, above which it is expected that the general population could experience notable discomforts which are not disabling and remain transient, to levels above which it is predicted that the general population could experience life-threatening health effects or death. The appropriate use of susceptible subpopulations such as children, elderly, and patients with defined diseases when deriving chemical-specific acute exposure levels is still a matter of controversy.

EU AETLs will speed up the harmonized implementation of the Seveso II directive on the control of major accident hazards involving dangerous substances. Nine partners belonging to research organizations and six European countries will participate in the work. Several innovative ideas, such as dose response modelling or toxicokinetics and toxicodynamics data will be used. A panel of experts from government and industry will be assembled and review the progress of the project.

REVIEW AND RESOLUTION OF COT/AEGL COMMENTS

Chloroform **CAS Reg. No. 67-66-3**

Chemical Manager: Steve Barbee, Arch Chem. Inc.
Staff Scientist: Robert Young, ORNL

Prior to Federal Register submission, the proposed chloroform AEGLs were revisited. Robert Young reviewed the previously proposed values and their rationale, and identified several items in need of discussion: (1) development of 10-minute values, (2) adjustment of existing values by use of time scaling default n values of 1 or 3 rather than 2, and (3) justification of developmental toxicity as the critical effect for developing AEGL-2 values (Attachment 7). The chloroform AEGLs were briefly reviewed by the NRC/COT Subcommittee on AEGLs several years ago at which time concern was informally expressed regarding the use of a developmental toxicity endpoint as the critical effect for AEGL-2 development. This concern had been expressed by several NAC/AEGL members as well. Embryotoxicity as a possible critical effect resulting from acute exposure to chloroform was discussed at some length. The animal data from the key study (Schwetz et al., 1974) were discussed in detail. The endpoint was considered to be justified for AEGL-2 development due to acknowledgment of this effect in previous toxicity assessments and reviews. The recommendation that no AEGL-1 values be developed was reaffirmed. Ten-minute AEGL-2 and AEGL-3 values were derived and AEGLs for all time points were recalculated using

an *n* of 1 or 3 for time scaling to longer or shorter time periods, respectively. Additionally, the interspecies uncertainty factor of 10 previously used to develop the AEGL-3 was reduced to 3 and justified by pharmacokinetic and pharmacodynamic data indicating that rodents are more susceptible to chloroform-induced toxicity than are humans (this was the same justification for its application to AEGL-2 values as originally and currently proposed). AEGL-2 values of 120 ppm, 80 ppm, 64 ppm, 40 ppm, and 29 ppm for 10 minutes, 30 minutes, 1 hour, 4 hours, and 8 hours, respectively were accepted. Toxic effects more commonly associated with chloroform (e.g., hepatic and renal toxicity) were also taken into account in development of the AEGL-2 values. The AEGL-3 values (based on a 3-fold reduction of a 4-hr LC₅₀ in rats) of 3100 ppm, 2200 ppm, 1700 ppm, 1100 ppm, and 540 ppm were also accepted. The extrapolation to 10-minutes was also justified by the fact that human experience data indicate that exposures as high as 22,500 ppm for approximately 30-120 minutes may be tolerated without fatal effects. A motion was made by Ernie Falke and seconded by Richard Niemeier to adopt the above AEGLs. The motion passed (YES:13 ; NO: 4; ABSTAIN: 1) (Appendix B). Revised TSD be circulated to NAC/AEGL.

Boron Trifluoride
CAS Reg. No. 353-42-4

Chemical Manager: George Rusch, Honeywell
Staff Scientist: Claudia Troxel, ORNL

The discussion was tabled to a later meeting because Honeywell may consider conducting a no-effect level irritation study in responding to COT/AEGL review comments.

Chlorine Trifluoride
CAS Reg. No. 7790-91-2

Chemical Manager: Bob Benson, US EPA
Staff Scientist: Sylvia Talmage, ORNL

The TSD for chlorine trifluoride, a severe respiratory irritant, was written in 1997. At that time the NAC/AEGL Committee considered time scaling the AEGL-1 values for respiratory irritants. Based on the fact that adaptation occurs to the slight irritation on which the AEGL-1 is usually based, the NAC/AEGL now uses the same value across all exposure durations. Therefore, the AEGL-1 values for chlorine trifluoride were revisited to update them before sending the TSD to the NRC/COT. The original AEGL-1 values were based on mild sensory irritation in the dog during an exposure to 1.17 ppm for 3 hours. Mild sensory irritation was considered a NOAEL for notable discomfort which defines the AEGL-1. This value was divided by interspecies and intraspecies uncertainty factors of 3 each for a total of 10. The resulting value is 0.12 ppm (Attachment 8). Rather than time scaling this value as was done in the original TSD, it was proposed to use 0.12 ppm across all exposure durations. It was moved by George Rodgers and seconded by Richard Thomas to accept 0.12 ppm across all AEGL-1 exposure durations. The motion passed (YES: 14; NO: 0; Abstain: 0) (Appendix C).

Toluene
CAS Reg. No. 108-88-3

Chemical Manager: Larry Gephart, Exxonmobil
Staff Scientist: Sylvia Talmage, ORNL

Sylvia Talmage discussed the review comments of the NRC/COT on toluene (Attachment 9). The NRC/COT basically felt that the derived interim values were inconsistent with the human data, especially those values derived for the longer-term exposures via time-scaling. They also suggested adding data that shows that many solvents, including toluene, rapidly reach equilibrium in the blood and brain, therefore, negating the need for time scaling. Furthermore, they rejected using the symptom of irritation as the basis for the AEGL-1 because many studies indicate that toluene is a pleasant-smelling, non-irritating chemical. The revised AEGL-1 was based on the preponderance of data from clinical and occupational exposures that indicate a concentration of 200 ppm would be without an effect that exceeds the definition of an AEGL-1. This value was proposed for all time periods as clinical studies indicate that this concentration of toluene rapidly reaches equilibrium in the blood and does not increase with increased exposure duration. No intraspecies uncertainty factor was applied as the value was based on several hundred individuals in clinical studies and several thousand individuals in occupational exposure studies. The motion was made by Bob Snyder and seconded by Ernie Falke to accept 200 ppm across all exposure durations. The motion passed (YES:13; NO: 2; Abstain:0) (Appendix D).

The revised interim AEGL-2 values were based on multiple studies that showed that exposure to 700 ppm for 20 minutes was a NOAEL for obvious central nervous system depression. Because equilibrium in the blood and brain may not be reached during the short exposure to this concentration, the value was time-scaled to the 10- and 30-minute exposure durations using the concentration:exposure duration relationship of $C^2 \times t = k$. The n value of 2 was based on multiple lethality studies with mice, the most sensitive species to the central nervous system effects of toluene (TSD dated NAC/Draft 5: 11/2002, Section 6.3. Derivation of AEGL-2). Based on similarity in structure and metabolism with the xylenes, the 1-hour AEGL-2 value was time scaled from the 30-minute value using a human pharmacokinetic model for xylene. Because steady state would be reached in the blood and brain within an hour, the 4- and 8-hour values were set equal to the 1-hour value (see table on page 9). It was moved by Bob Snyder and seconded by Ernie Falke to accept the proposed AEGL-2 values. The motion passed (YES: 14 ; NO: 1; Abstain: 0) (Appendix D).

The revised interim AEGL-3 values were based on the highest NOAEL in several rat and mouse studies. The NOAEL for lethality of 6250 ppm for 2 hours is supported by several other studies. Interspecies and intraspecies uncertainty factors of 1 and 3, respectively, were considered adequate as, in the first case, uptake is greater in small rodent species than in humans; and, in the second case, the minimum alveolar concentration differs by no more than 3 among the human population. Time scaling utilized $n = 2$ as above for the AEGL-2. Because the time-scaled 8-hour value of 1000 ppm was inconsistent with the human data, the 8-hour value was set equal to the 4-hour value. The motion to accept the proposed values was made by Bob Snyder and seconded by Ernie Falke. The motion passed (YES: 11; NO: 1; Abstain: 3) (Appendix D).

Summary of Interim AEGL Values for Toluene [ppm]						
Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint
AEGL-1	200	200	200	200	200	NOAEL for definition of AEGL-1, multiple clinical studies
AEGL-2	990	570	510	510	510	NOAEL for obvious central nervous system depression in humans
AEGL-3	7200	4200	2900	1500	1500	Highest NOAEL for lethality in studies with rats and mice

REVIEW OF PRIORITY CHEMICALS FOR AEGL VALUES

1,4-Dioxane CAS Reg. No. 123-91-1

Chemical Manager: Jim Holler, ATSDR
Staff Scientist: Peter Griem, FoBiG

The chemical review was presented by Peter Griem (Attachment 10). Dioxane is produced at about 10,000 tons per year and is mainly used as a processing solvent. The majority of the available human and animal studies have been carried out more than 60 years ago. The pharmacokinetic study of Young et al. (1977) was discussed as the key study for AEGL-1. Four healthy young men were exposed to 50 ppm for 6 hours. Eye irritation was a frequent complaint throughout exposure. Since the authors considered 50 ppm an adequate workplace standard, the irritant effect was estimated to have been weak. This conclusion is supported by older volunteer studies (Silverman et al., 1946; Wirth and Klimmer, 1936) in which exposure levels of about 300 ppm only induced slight to moderate irritation. Since for local effects to the eyes, no toxicokinetic differences exist between individuals, a reduced intraspecies uncertainty factor of 3 was applied. Because the eye irritation was not reported to have increased with time in the key study, which is also supported by a guinea pig study (Yant et al., 1930), the 17 ppm concentration was used across all AEGL-1 exposure durations. A motion was made by Bob Benson and seconded by Jim Holler to adopt the 17 ppm concentration for all AEGL-1 time points. The motion passed (YES:17; NO: 0; Abstain:1) (Appendix E).

As additional information for emergency responders, a level of distinct odor awareness was derived. On a standardized 5-step scale of odor intensity, the level of distinct odor is between the level of faint odor and the level of strong odor. Based on a reported odor detection threshold of 0.8 ppm (Hellman and Small, 1974) and the threshold of 0.3 ppm for the reference chemical n-butanol measured in the same study, a corrected odor threshold of 0.11 ppm (using the reference odor threshold of 0.04 ppm for n-butanol) was derived. By application of a default factor of 16, a level of distinct odor awareness of 1.7 ppm was calculated. At this level about 50 percent of the

population are expected to experience a distinct odor. Assuming log-normal distribution, the 10- and 90-percentile concentrations for distinct odor awareness are 0.34 ppm and 8.8 ppm, respectively. A motion was made by Nancy Kim and seconded by Dave Belluck to adopt a level of distinct odor awareness of 1.7 ppm. The motion passed (YES:18; NO: 0; Abstain:1) (Appendix E).

With regard to the AEGL-2, both effects on the central nervous system and effects on the liver were discussed. In a study by Goldberg et al. (1964), exposure of rats to 6000 ppm for 4 hours resulted in a significant decrease of a conditioned response (pole climbing in response to buzzer to avoid electrical shock), but did not affect the escape behavior (pole climbing in response to electrical shock without buzzer). This level was considered an adequate starting point because at 8300 ppm for 3.5 hours, narcosis was observed in mice (Wirth and Klimmer, 1936). A total uncertainty factor of 30 was applied. The intraspecies factor was reduced to 3 because application of the default factor would lower the AEGL-2 values to a level that was used in the pharmacokinetic study by Young et al. (1977); i.e., a level that humans are known to tolerate without adverse effect. An interspecies factor of 10 was applied. Due to the lack of chemical-specific data, time extrapolation was done using the default values for the exponent n (1 for longer and 3 for shorter time periods). Time extrapolation was continued to the 10-minute period because even at the considerably higher concentrations of 1600 ppm for 10 minutes (Yant et al., 1930) or 1400 ppm for 5 minutes (Wirth and Klimmer, 1936) exposed human subjects did not experience more severe effects than irritation. In the study by Drew et al. (1978) slight liver damage in rats was indicated by a two- to threefold increase in the serum levels of three liver enzyme activities following an exposure to 2000 ppm for 4 hours. The endpoint of hepatotoxicity was also considered relevant because liver necrosis occurred in cases of fatal dioxane exposure at the workplace and repeated liver cytotoxicity is the mechanism suggested as the mechanism of the carcinogenic effect of dioxane. Application of a total uncertainty factor of 10 (3 for interspecies and 3 for intraspecies uncertainty factors) based on the same reasoning as above and, additionally, on the fact that the observed effect was considered below the level that could be tolerated according to the AEGL-2 definition and application of time extrapolation as above results in exactly the same AEGL-2 values. A motion was made by Loren Koller and seconded by Mark McClanahan to adopt AEGL-2 values for 1,4-dioxane for 10 minutes to 8 hours of 580 ppm, 400 ppm, 320 ppm, 200 ppm and 100 ppm. The motion passed (YES: 18; NO: 0; Abstain: 0) (Appendix E).

The AEGL-3 values were based on a 4-hour LC_{50} of 14300 ppm in rats (Pozzani et al., 1959). Although this study did not use the most sensitive species (cats), it was used as key study because it was the only study that was adequately described in the publication. A factor of 3 was used for extrapolation to a LC_{01} . A total uncertainty factor of 10 (3 for interspecies and 3 for intraspecies uncertainty factors) was applied because a higher uncertainty factor would have resulted in AEGL-3 values of 480 ppm for 10 and 30 minutes, which contrasts with the observation that exposure of human subjects to 1600 ppm for 10 minutes (Yant et al., 1930) resulted in moderate irritation, but not in more severe effects. Due to the lack of chemical-specific data, time extrapolation was done using the default values for the exponent n (1 for longer and 3 for shorter time periods). It was moved by Steve Barbee and seconded by Mark McClanahan to adopt AEGL-3 values for 1,4-

dioxane for 10 minutes to 8 hours of 950 ppm, 950 ppm, 760 ppm, 480 ppm, and 240 ppm. The motion passed (YES:17; NO: 1; Abstain:0) (Appendix E).

SUMMARY OF AEGL VALUES FOR 1,4-DIOXANE						
Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint
AEGL-1	17 ppm (60 mg/m ³)	17 ppm (60 mg/m ³)	17 ppm (60 mg/m ³)	17 ppm (60 mg/m ³)	17 ppm (60 mg/m ³)	Slight eye irritation in humans (Young et al., 1977)
AEGL-2	580 ppm (2100 mg/m ³)	400 ppm (1400 mg/m ³)	320 ppm (1100 mg/m ³)	200 ppm (720 mg/m ³)	100 ppm (360 mg/m ³)	Slight behavioral effects (Goldberg et al., 1964), slight liver cytotoxicity (Drew et al., 1978) in rats
AEGL-3	950 ppm (3400 mg/m ³)	950 ppm (3400 mg/m ³)	760 ppm (2700 mg/m ³)	480 ppm (1700 mg/m ³)	240 ppm (860 mg/m ³)	No deaths in rats (4 hours) (Pozzani et al., 1959)
Level of distinct odor awareness					1.7 ppm (6.1 mg/m ³)	Odor detection threshold in humans (Hellman and Small, 1977)

Sulfur Dioxide
CAS Reg. No. 7446-09-5

Chemical Manager: Loren Koller, OSU
Staff Scientist: Cheryl Bast, ORNL

The discussion on sulfur dioxide was led by Cheryl Bast (Attachment 11). An AEGL-1 of 0.25 ppm was proposed based on the weight-of-evidence from several studies with exercising asthmatics. This value was a NOAEL for bronchoconstriction in exercising asthmatics. A motion to accept the AEGL-1 was made by Loren Koller and seconded by Mark McClanahan. The motion passed (YES:16; NO: 0; Abstain:1) (Appendix F). It was noted that the Shepard et al. (1981) and Linn et al. (1987) studies should be added to the weight-of-evidence argument. It was further noted that 0.25 ppm is a NOAEL for clinical symptoms, that this lack of response occurs in cool, dry air, and that the data do not include studies out to 8 hours.

An AEGL-2 of 1.0 ppm across time was proposed based on a weight-of-evidence approach. The endpoint was an increase in airway resistance of 102%-580% in exercising asthmatics exposed to 1.0 ppm. It was moved by Ernest Falke and seconded by Loren Koller to accept this value. The motion did not pass (YES: 8; NO: 8 ; Abstain: 0) (Appendix F). Following further discussion on the short time periods of the studies and lack of exercise in one of the studies, values of 1.0, 1.0, 1.0, 0.75, and 0.75 ppm were proposed by Richard Thomas. The 0.75 ppm value was considered a NOAEL for the longer time periods. The motion was seconded by Robert Snyder. The motion passed (YES: 12; NO: 3; Abstain: 2) (Appendix F). It was suggested that data on atopic individuals be added to the justification.

The data leading to derivation of AEGL-3 values was discussed by Cheryl Bast. The discussion included the reason for time scaling, the mechanism of action of sulfur dioxide, and the *n* value of 4 derived from mouse lethality data. Jonathan Borak pointed out that the response for the AEGL-3 burns and constriction of the bronchi - would be the same for asthmatics and non-asthmatics. The benchmark dose approach was utilized (using the 5% response of the lower 95% confidence interval). The lethality data from a 4-hour study with rats was used. The total uncertainty factor was 30. It was moved by Ernest Falke and seconded by Bob Benson to accept the values. The motion passed (YES: 13; NO: 3; Abstain: 1) (Appendix F).

Summary of Proposed AEGL Values for Sulfur Dioxide [ppm]						
Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint
AEGL-1	0.25	0.25	0.25	0.25	0.25	NOAEL for clinical symptoms in exercising asthmatics
AEGL-2	1.0	1.0	0.75	0.75	0.75	NOAEL for severe respiratory response in exercising asthmatics
AEGL-3	42	32	27	19	16	Benchmark dose approach; 4-hour study with the rat

Dimethyldichlorosilane: CAS Reg. No. 75-78-5

Methyltrichlorosilane: CAS Reg. No. 75-79-6

Trimethylchlorosilane: CAS Reg. No. 75-77-4

Chemical Manager: Ernie Falke, EPA

Staff Scientist: Cheryl Bast, ORNL

Cheryl Bast reminded the NAC/AEGL Committee that acute toxicity from dimethyldichlorosilane and methyltrichlorosilane is due to the hydrolysis product, HCl.(Attachment 12) Because the 4- and 8-hour AEGL-2 values as well as the 8-hour AEGL-3 value for HCl were modified in response to NRC/COT comments, the respective values for the two silanes needed modification. Therefore, it was proposed that for dimethyldichlorosilane the 4-hour AEGL-2 value be raised from 3.3 to 6.5 ppm, that the 8-hour AEGL-2 value be set equal to the 4-hour value, and that the 8-hour AEGL-3 value be set equal to the 4-hour AEGL-3 value of 13 ppm. It was moved by John Hinz and seconded by Nancy Kim to accept the proposed changes. The motion passed (YES:17; NO: 0; Abstain: 0) (Appendix G).

A similar change was proposed for methyltrichlorosilane. The 4- and 8-hour AEGL-2 values were raised to 3.1 and 3.1 ppm and the 8-hour AEGL-3 value was set equal to the 4-hour value of 7.0 ppm. The motion to accept these changes was made by John Hinz and seconded by George Rodgers. The motion passed (YES:16; NO: 0; Abstain:0) (Appendix H). The statement that the values are conservative will be changed to say that the previous values were inconsistent with the human data.

For trimethylchlorosilane, the proposed AEGL-1 value of 1.8 ppm was based on its breakdown to 1 mole of hydrogen chloride (Attachment 13). This 1.8 ppm concentration of hydrogen chloride was a NOAEL for pulmonary function changes in exercising asthmatics. The motion to accept 1.8 ppm across all AEGL-1 exposure durations as well as the proposed values for the AEGL-2 and AEGL-3 was made by John Hinz and seconded by Mark McClanahan. The motion passed (YES:18; NO:1; Abstain:0)(Appendix I). The proposed AEGL-2 values were based on severe eye and respiratory tract irritation in rats exposed to 3171 ppm for 1 hour. Intraspecies and intraspecies uncertainty factors of 10 and 3 were applied, and a modifying factor of 3 was applied, the latter to account for data in a single species and use of a LOAEL. The total adjustment was 100. Time scaling utilized the same value as calculated for hydrogen chloride ($n = 1$). Based on the extensive scrubbing of hydrogen halides by the respiratory tract, the 4- and 8-hour values were set equal as was done for hydrogen chloride. Values are listed in the table below. The motion for AEGL-2 passed (YES:19; NO:0; Abstain:1) (Appendix I). The AEGL-3 was based on a calculated LC_{01} of 3970 ppm in rats exposed to trimethylchlorosilane for 1 hour. Interspecies and intraspecies uncertainty factors of 10 and 3 were applied, and time scaling was based on $n = 1$. The 4- and 8-hour values were set equal as was done for hydrogen chloride. The motion for AEGL-3 was also passed (YES:19; NO: 0; Abstain: 1)(Appendix I). It should be noted that the values may be conservative as the hydrolysis of trimethylchlorosilane may not be complete.

Summary of Proposed AEGL Values for Trimethylchlorosilane [ppm]						
Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint
AEGL-1	1.8	1.8	1.8	1.8	1.8	NOAEL for clinical symptoms in exercising asthmatics (based on hydrolysis to hydrogen chloride)
AEGL-2	192	64	32	16	16	Severe respiratory response in rats adjusted by modifying factor
AEGL-3	790	270	130	33	33	Calculated 1-hour LC_{01} in rats

Nitrogen Dioxide
CAS Reg. No. 10102-44-0

Chemical Manager: Loren Koller, OSU
Staff Scientist: Carol Forsyth, ORNL

Ed Faeder, SRF Environmental, Inc., made a presentation entitled "Surface Coal Mining in Wyoming – an NO_2 Exposure Issue" (Attachment 14) along with representatives Terri Lorenzon, State of Wyoming, Wendy Hutchinson, Thunder Basin Coal Wyoming Environmental Quality Council, and Blair Gardener, Jackson Kelly, PLLC.

More than one-third of all the coal mined in the United States during fiscal year 2002 was produced from surface mines in the state of Wyoming. It is mined by removing rock and other material overlying the coal seam(s), fracturing, extracting, and crushing the coal, and loading it into railcars for shipment. Much of the mining process involves the use of explosive charges to fracture the coal and overburden to facilitate coal extraction. For a variety of reasons, the explosive of choice is a mixture of ammonium nitrate and fuel oil ("ANFO"). Hundreds of millions of pounds of ANFO are used annually in the production processes. The blasting operation ideally converts ANFO into nitrogen, carbon dioxide, and water. However, under real-world conditions, combustion of ANFO is incomplete and a variety of by-products are formed including oxides of nitrogen. Nitrogen dioxide ("NO₂") can form in sufficient quantities and concentrations to be seen as a red or orangish-brown cloud, under certain conditions. By regulating the blasting processes, as mines currently do, the likelihood of high levels of NO₂ impacting a single receptor more than once *in a long time* is low. This translates to the likelihood that a given human is exposed to a *high* level of NO₂ for more than a *short* time is very *infrequent*.

The purpose for this talk was to present their opinions on the development of AEGLs to the National Advisory Committee ("Committee"), and solicit input through the development of realistic AEGL-1 and AEGL-2 10-minute values. From a public safety standpoint, the distinction between *noticeable detectability* and *notable discomfort* is quite important. If the AEGL-1 level is set at this notable discomfort threshold, it could assist Wyoming officials charged with responsibility of promoting the safety of individuals who might be exposed. It could also help the Committee understand the application of AEGL values to actual settings. To the extent that the 10-minute AEGL-1 value reflects notable physiologic changes in people or organoleptic detectability, rather than modest discomfort, that value becomes more significant for the establishment of an exposure criterion "not to be exceeded more than once in a long time" than the 10-minute AEGL-2 value.

Nitrogen Dioxide TSD Discussion:

Previous NAC/AEGL action on nitrogen dioxide was reviewed and current concerns were addressed in a presentation by Carol Forsyth (Attachment 15). On September 15, 1998, the NAC/AEGL had adopted by unanimous vote the 30-minute, 1-, 4-, and 8-hour values for all three AEGL levels. At a subsequent meeting, a concern was expressed by the committee that the basis for AEGL-2, Henschler et al., 1960, was a secondary citation. It was explained that the study was translated, details were added to the TSD, and that the development team believed this to be a well-conducted study. Another concern was for the quality of the study used as the basis for AEGL-3, Henry et al., 1969. The development team considers this to be a well-conducted study and the lead author is respected in the field of inhalation toxicology; some details have been added to the TSD. No additional concerns were raised by the NAC/AEGL following this discussion. Derivation of the 10-minute values followed the SOP, used previously accepted key studies and endpoints, are supported by human and animal data, and time-scaled for AEGL-2 and -3 because the key studies had exposure durations ≤ 2 hours. The 10-minute values for all three AEGL levels were then proposed by Bob Benson and seconded by Tom Hornshaw as 0.50, 20, 34 ppm for AEGL-1, 2, and 3, respectively. The motion was voted separately and passed with majority votes (AEGL-1: YES: 14; NO:4; Abstain:0, AEGL-2: YES: 14; NO:3; Abstain: 1, and AEGL-3:

YES:17; NO: 0; Abstain: 1) (Appendix J). The NAC/AEGL requested the following of the development team: (1) add back-up/supporting information for AEGL-2 and -3 as suggested by Steve Barbee; (2) include the magnitude of the decrease in arterial pO₂ measured in COPD individuals; (3) evaluate information presented at the meeting by George Alexeef; and, (4) resend the TSD to the committee after these revisions are completed.

Summary of AEGL Values (ppm [mg/m ³])					
AEGL Level	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1	0.50 [0.94]	0.50 [0.94]	0.50 [0.94]	0.50 [0.94]	0.50 [0.94]
AEGL-2	20 [38]	15 [28]	12 [23]	8.2 [15]	6.7 [13]
AEGL-3	34 [64]	25 [47]	20 [38]	14 [26]	11 [21]

Nitric Oxide
CAS Reg. No. 10102-43-9

Chemical Manager: Loren Koller, OSU
Staff Scientist: Carol Forsyth, ORNL

Carol Forsyth briefly pointed out (Attachement 15) that on September 15, 1998, the NAC/AEGL voted to adopt the nitrogen dioxide values for nitric oxide because the major effects are from nitrogen dioxide. A note will be included in the nitric oxide (NO) TSD that short-term exposures below 80 ppm NO should not constitute a health hazard. No additional discussions or comments were made by the NAC/AEGL Committee.

Carol expressed concern on the AEGLs development of Nitric acid (Attachment 15) and proposed the AEGLs as stated in the current TSD or to develop alternatives. A report summarized the study of Gray et al. (1954) by W. F. ten Berge was suggested for incorporation if it is appropriate. A revised TSD will be presented at the next meeting.

Benzene
CAS Reg. No. 71-43-2

Chemical Manager: Bob Snyder, Rutgers University
Staff Scientist: Marcel van Raaij, RIVJM, The Netherlands

Benzene was discussed for the third time (Attachment 16). The TSD of benzene was only modified at some specific points. First, this includes the addition of studies described by Von Oettingen in 1940 with various C x T combinations resulting in narcosis. These studies provide evidence for N= ±1.

It is proposed not to use these data directly but to use these data to support the concept that $n=3$ for extrapolating to shorter duration is too conservative and that $n=2$ is a good alternative. Secondly, a general paragraph on occupational exposure was prepared to be added to the TSD.

In the NAC/AEGL-26 (June 2002), John Morawetz made comments on the human studies in the TSD and urged for a rewrite. In addition, Exxon and API offered to provide additional data on human / occupational exposure (and health effects). No additional data on acute exposure data were received by the December 2002 meeting.

Because no decisions were made on the selection of endpoints that should be used for AEGL development at the June 2002 meeting, the current TSD did not reflect a total rewrite. The NAC/AEGL considered irritation and mild CNS effects endpoints for developing possible AEGL-1 values. First, a study by Sbrova 1950 (110 ppm, 2 h, no subjective symptoms) was considered as a NOAEL for irritation. That would have resulted in 37 ppm as AEGL-1 for all exposure time periods. A motion was made by Ernie Falke and seconded by George Rodgers to adapt the proposed 37 ppm for AEGL-1. The motion failed (YES:5; NO: 7; Abstain: 1) (Appendix H). Alternatively, the NAC/AEGL considered mild CNS effects for AEGL-1. The interspecies factor was 1, the intraspecies factor was 3 since CNS effects do not vary more than a factor 2-3 within the population. N-values were 2 (to shorter duration) and 1 (to longer durations). The resulting AEGL-values were: 127, 73, 52, 18, and 9 for 10-min., 30-min, 1, 4, and 8 h, respectively. A motion was made by John Hinz and seconded by Mark McClanahan to accepted the proposed AEGL values. The motion for AEGL-1 passed (YES: 11; NO: 0; ABSTAIN: 1) (Appendix H)".

Toward the end of the meeting, there was not a quorum to vote for the AEGL-2 and AEGL-3 values. However, NAC/AEGL continued to discuss the choices and the approach to be taken for the AEGL-2 and AEGL-3 levels. It was concluded that for acute exposure, CNS effects are the endpoint to be used and that no values should be developed based on hematotoxicity or developmental toxicity. Similar to toluene (which has been reviewed already by the COT), the developmental effects of benzene appear to be similar to an "alcohol-like" pattern of effects on the fetus which is most likely the consequence of repeated exposure.

The committee members were supportive of the approach presented in the TSD for AEGL-2 and 3 values including the use of $n=2$ and $n=1$ (see above). (Because the default values for n are 3 and 1, the only significant change for benzene is the use of $n = 2$ rather than the default value of 3 when time scaling to shorter time periods.) In addition, the NAC/AEGL present had a rather uniform opinion and supported the historic value of all occupational exposure data providing a picture on benzene exposure and health effects were provided and distributed to NAC/AEGL prior to the meeting. It was acknowledged that many of the "old" studies do not fulfill current SOP criteria but that the concentrations reported in different factories and workplaces, and the number of people involved, provides insight on the order of magnitude of the exposure. Such conditions were not associated with an inability to escape. The TSD of benzene will be reviewed at a future meeting.

John Morawetz was unable to attend the NAC/AEGL-27 meeting; however, he sent his comments regarding his pre-meeting review of benzene TSD and submitted his comment (Attachment 17) and requested to be noted in the meeting highlights as the following:

“Mr. Morawetz sent comments describing a number of serious problems with the characterizations of many of the human studies described in the Benzene TSD and summarized in the Derivation Sections for AEGL-1, 2 and 3. Mr. Morawetz requested that the committee decide if any changes in the descriptions of the human studies need to be made and communicate to him that decision.”

Administrative Matters

Dr. Oscar Hernandez provided an update on the human subject study clearance status and distributed two handouts: *Environmental News- Agency requests National Academy of Sciences (NAS)* input on consideration of certain human toxicity studies (Attachment 18) And the scope of NAS project “Use of Third Party Toxicity Research with Human Research Participant.” (Attachment 19). In addition, George Rusch asked NAC/AEGL members to comment on the Draft write up “Application of Acute Exposure Guideline Levels” (Attachment 20) and send comments to him since this is the first time the Committee got a chance to read it and the discussion was deferred to a later meeting.

The site and time of the next meeting, NAC/AEGL-28 was discussed. Pending the availability of the meeting facility at Salt Lake City, Utah and EPA off-site travel approval, the meeting will be held in conjunction with the SOT Annual Meeting. The date is set for March 7-9, 2003, at Salt Lake City, Utah. The alternate proposal was on March 25-27, 2003, in Washington, DC. The dates for NAC/AEGL-29 and 30 have been set tentatively on June 17-19, and September 16-18, 2003, respectively. More information regarding the NAC/AEGL-28 will be coming from Po-Yung Lu as soon as the determination and decision is made.

All items in the agenda were discussed as thoroughly as the time permitted. The meeting highlights were prepared by Po-Yung Lu and Sylvia Talmage, Oak Ridge National Laboratory, with input from the respective Chemical Managers, authors, and other contributors.

LIST OF ATTACHMENTS

The attachments were distributed during the meeting and will be filed in the EPA Docket Office.

- Attachment 1. NAC/AEGL-27 Meeting Agenda
- Attachment 2. NAC/AEGL-27 Attendee List
- Attachment 3. Summary Category V chemicals: Critical Health Effect Starting Points for AEGL Determination: LOAEL vs. NOAEL
- Attachment 4. Summary Report of LOA Subcommittee
- Attachment 5. Summary Report of Application of Ratios for Determination of AEGLs
- Attachment 6. Acute Toxicity Threshold for Land Use Planning
- Attachment 7. Data Analysis and Response to COT/AEGL Comments of Chloroform
- Attachment 8. Data Analysis and Response to COT/AEGL Comments of Chlorine Trifluoride
- Attachment 9. Data Analysis and Response to COT/AEGL Comments of Toluene
- Attachment 10. Data Analysis of 1,4-Dioxane
- Attachment 11. Data Analysis of Sulfur Dioxide
- Attachment 12. Data Analysis of Dimethyldichlorosilane and Methyltrichlorosilane
- Attachment 13. Data Analysis of Trimethylchlorosilane
- Attachment 14. Surface Coal Mining in Wyoming - an NO₂ Exposure Issue
- Attachment 15. Data Analysis of Nitrogen dioxide and Nitric acid
- Attachment 16. Note on Benzene from John Morawetz
- Attachment 17. Data Analysis of Benzene
- Attachment 18. EPA Environmental News
- Attachment 19. Scope of NAS Project Study: Use of Third Party Toxicity Research with Human Research Participant
- Attachment 20. Application of Acute Exposure Guideline Levels - Draft

LIST OF APPENDICES

- Appendix A. Revised meeting highlights of NAC/AEGL-26 (sent to NAC/AEGL on 12/26/2002 by E-mail).
- Appendix B. Ballot for Chloroform
- Appendix C. Ballot for Chlorine Trifluoride
- Appendix D. Ballot for Toluene
- Appendix E. Ballot for 1,4-Dioxane
- Appendix F. Ballot for Sulfur Dioxide
- Appendix G. Ballot for Dimethyldichlorosilane
- Appendix H. Ballot for Methyltrichlorosilane
- Appendix I. Ballot for Trimethylchlorosilane
- Appendix J. Ballot for Nitrogen Dioxide
- Appendix K. Ballot for Benzene

Accept Report on Iron Pentacarbonyl + entire report
 March 3, 2003 "STATUS REPORT ON NOAEL/LOAEL
 CONSISTENCY CONCERNS FOR AEGL DEVELOPMENT"

NAC/AEGL Meeting 28: March 7-8, 2003

Appendix B

Chemical:

CAS Reg. No.:

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	Y			Nancy Kim	Y		
Steven Barbee	Y			Loren Koller	Y		
Lynn Beasley	A	A	A	Glenn Leach	A	A	A
David Belluck	A			Mark McClanahan	Y		
Robert Benson	Y			John Morawetz	Y		
Jonathan Borak	A	A	A	Richard Niemeier	A		
William Bress	Y			Marinelle Payton	Y		
George Cushmac	A			Zarena Post	A	A	A
Al Dietz	A	A	A	George Rodgers	Y		
Ernest Falke	Y			George Rusch, Chair	Y		
Larry Gephart	A			Robert Snyder	Y		
John Hinz	Y			Thomas Sobotka	A	A	A
Jim Holler	Y			Kenneth Still	A	A	A
Thomas Hornshaw	Y			Richard Thomas	Y		
				TALLY	17/17		

PPM, (mg/m ³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	, ()	, ()	, ()	, ()	, ()
AEGL 2	, ()	, ()	, ()	, ()	, ()
AEGL 3	, ()	, ()	, ()	, ()	, ()

AEGL 1 Motion: Alexeeff Second: Bress

AEGL 2 Motion: _____ Second: _____

AEGL 3 Motion: _____ Second: _____

Approved by Chair: _____ DFO: Paul S. Miller Date: 3/8/03

Appendix C

NAC/AEGL Meeting 28: March 7-8, 2003

Chemical: *Morawetz Occupational Studies* CAS Reg. No.:

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff				Nancy Kim			
Steven Barbee				Loren Koller			
Lynn Beasley	A	A	A	Glenn Leach	A	A	A
David Belluck				Mark McClanahan			
Robert Benson				John Morawetz			
Jonathan Borak	A	A	A	Richard Niemeier			
William Bress				Marinelle Payton			
George Cushmac				Zarena Post	A	A	A
Al Dietz	A	A	A	George Rodgers			
Ernest Falke				George Rusch, Chair			
Larry Gephart				Robert Snyder			
John Hinz				Thomas Sobotka	A	A	A
Jim Holler				Kenneth Still	A	A	A
Thomas Hornshaw				Richard Thomas			
				TALLY			

1. Breathing zone samples are the preferred estimate of worker's exposure. All breathing zone samples should be described as such.

PPM, (mg/m ³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	, ()	, ()	, ()	, ()	, ()
AEGL 2	, ()	, ()	, ()	, ()	, ()
AEGL 3	, ()	, ()	, ()	, ()	, ()

2. Area, general workplace, bulk samples & theoretical calculations from bulk samples should be clearly described as such.

AEGL 1 Motion: _____ Second: _____

AEGL 2 Motion: _____ Second: _____

AEGL 3 Motion: _____ Second: _____

Approved by Chair: *[Signature]*

DFO: *Paul Win*

Date: *3/7/03*

Unanimous support by the Committee

Appendix D

NAC/AEGL Meeting 28: March 7-8, 2003

Chemical: 1/204 ^{PENTA-}CARBONYL

CAS Reg. No.:

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff			Y	Nancy Kim			Y
Steven Barbee			Y	Loren Koller			Y
Lynn Beasley	A	A	A	Glenn Leach	A	A	A
David Belluck			A	Mark McClanahan			Y
Robert Benson			Y	John Morawetz			Y
Jonathan Borak	A	A	A	Richard Niemeier			A
William Bress			Y	Marinelle Payton			Y
George Cushmac			Y	Zarena Post	A	A	A
Al Dietz	A	A	A	George Rodgers			Y
Ernest Falke			Y	George Rusch, Chair			Y
Larry Gephart			A	Robert Snyder			Y
John Hinz			Y	Thomas Sobotka	A	A	A
Jim Holler			Y	Kenneth Still	A	A	A
Thomas Hornshaw			Y	Richard Thomas			Y
				TALLY			18/18

PPM, (mg/m ³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	, ()	, ()	, ()	, ()	, ()
AEGL 2	, ()	, ()	, ()	, ()	, ()
AEGL 3	3.6 , ()	1.2 , ()	0.60 , ()	0.15 , ()	0.075 , ()

Note to re-affirm earlier balloted numbers, incorporating discussion of NOEL as departure point for AEGL-3.
 AEGL 1 Motion: _____ Second: _____

AEGL 2 Motion: _____ Second: _____

AEGL 3 Motion: Koller Second: McClanahan

Approved by Chair: [Signature] DFO: Pauls Min Date: 3/7/03

Appendix E

NAC/AEGL Meeting 28: March 7-8, 2003

Chemical: IRON PENTACARBONYL

CAS Reg. No.:

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff		N		Nancy Kim		Y	
Steven Barbee		Y		Loren Koller		Y	
Lynn Beasley	A	A	A	Glenn Leach	A	A	A
David Belluck		A		Mark McClanahan		Y	
Robert Benson		Y		John Morawetz		P	
Jonathan Borak	A	A	A	Richard Niemeier		A	
William Bress		Y		Marinelle Payton		Y	
George Cushmac		Y		Zarena Post	A	A	A
Al Dietz	A	A	A	George Rodgers		Y	
Ernest Falke		Y		George Rusch, Chair		Y	
Larry Gephart		A		Robert Snyder		Y	
John Hinz		Y		Thomas Sobotka	A	A	A
Jim Holler		Y		Kenneth Still	A	A	A
Thomas Hornshaw		P		Richard Thomas		Y	
				TALLY		15/16	

PPM, (mg/m ³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	, ()	, ()	, ()	, ()	, ()
AEGL 2	1.2, ()	0.40, ()	0.20, ()	0.050, ()	0.025, ()
AEGL 3	, ()	, ()	, ()	, ()	, ()

AEGL 1 Motion: _____ Second: _____

AEGL 2 Motion: Koller Second: Hinz

AEGL 3 Motion: _____ Second: _____

Approved by Chair: [Signature] DFO: [Signature] Date: 3/8/03

Appendix F

NAC/AEGL Meeting 28: March 7-8, 2003

Chemical: *ETHYLENIMINE*

CAS Reg. No.:

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	Y			Nancy Kim	Y		
Steven Barbee	Y			Loren Koller	Y		
Lynn Beasley	A	A	A	Glenn Leach	A	A	A
David Belluck	A			Mark McClanahan	Y		
Robert Benson	Y			John Morawetz	Y		
Jonathan Borak	A	A	A	Richard Niemeier	A		
William Bress	Y			Marinelle Payton	Y		
George Cushmac	Y			Zarena Post	A	A	A
Al Dietz	A	A	A	George Rodgers	A		
Ernest Falke	Y			George Rusch, Chair	Y		
Larry Gephart	A			Robert Snyder	Y		
John Hinz	P			Thomas Sobotka	A	A	A
Jim Holler	Y			Kenneth Still	A	A	A
Thomas Hornshaw	Y			Richard Thomas	Y		
				TALLY	19/6		

PPM, (mg/m ³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	, ()	, ()	, ()	, ()	, ()
AEGL 2	, ()	, ()	, ()	, ()	, ()
AEGL 3	, ()	, ()	, ()	, ()	, ()

11 ppm = LOA (Level of Odor Awareness)

AEGL 1 Motion: Falke Second: Thomas

AEGL 2 Motion: _____ Second: _____

AEGL 3 Motion: _____ Second: _____

Approved by Chair: [Signature] DFO: Paul S. Miller Date: 3/9/03

Appendix G

NAC/AEGL Meeting 28: March 7-8, 2003

Chemical:

PIPERIDINE

LEA

CAS Reg. No.:

110-89-4

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	Y	N Y	Y	Nancy Kim	Y	Y Y	Y
Steven Barbee	Y	Y N	Y	Loren Kolier	A	A A	A
Lynn Beasley	A	A A	A	Glenn Leach	A	A A	A
David Belluck	A	A A	A	Mark McClanahan	A	A A	A
Robert Benson	Y	P N	Y	John Morawetz	N	N Y	P
Jonathan Borak	A	A A	A	Richard Niemeier	A	A A	A
William Bress	Y	N Y	Y	Marinelle Payton	Y	N Y	P
George Cushman	Y	N Y	Y	Zarena Post	A	A A	A
Al Dietz	A	A A	A	George Rodgers	A	A A	A
Ernest Falke	Y	Y Y	Y	George Rusch, Chair	Y	Y P	Y
Larry Gephart	A	A A	A	Robert Snyder	Y	Y Y	Y
John Hinz	Y	Y Y	Y	Thomas Sobotka	A	A A	A
Jim Holler	Y	Y Y	Y	Kenneth Still	A	A A	A
Thomas Hornshaw	Y	Y P	Y	Richard Thomas	Y	N Y	Y
				TALLY	14/15	8/14	13/13

PPM, (mg/m ³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	10 . ()	10 . ()	6.6 . ()	2.6 . ()	1.7 . ()
AEGL 2	100 . (*50)	100 . (*80)	66 . (*33)	26 . (*13)	17 . (*8.5)
AEGL 3	370 . ()	180 . ()	110 . ()	45 . ()	28 . ()

motion TO SET
original VALUES (HINE, KIM) - UNANIMOUS

AEGL 1 Motion: Snyder Second: Kim

AEGL 2 Motion: Snyder * R. Thomas Second: Hinz * John Hinz

AEGL 3 Motion: Alexeeff Second: Hinz

Approved by Chair: _____ DFO: Paul S. John Date: 3/8/03

* Second try Rashed.
LOA = 5.8 (Thomas/Kim) 12/13 positive (passed)

Appendix H

NAC/AEGL Meeting 28: March 7-8, 2003

Chemical: CARBON DISULFIDE

CAS Reg. No.: 75-15-0

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	Y	N		Nancy Kim	Y	Y	
Steven Barbee	Y	Y		Loren Koller	A	Y	
Lynn Beasley	A	A	A	Glenn Leach	A	A	A
David Belluck	A	A		Mark McClanahan	Y	N	
Robert Benson	Y	Y		John Morawetz	Y	Y	
Jonathan Borak	A	A	A	Richard Niemeier	A	A	
William Bress	Y	Y		Marinelle Payton	Y	Y	
George Cushmac	Y	Y		Zarena Post	A	A	A
Al Dietz	A	A	A	George Rodgers	Y	Y	
Ernest Falke	Y	Y		George Rusch, Chair	Y	Y	
Larry Gephart	A	A		Robert Snyder	Y	Y	
John Hinz	Y	Y		Thomas Sobotka	A	A	A
Jim Holler	Y	Y		Kenneth Still	A	A	A
Thomas Hornshaw	Y	Y		Richard Thomas	Y	Y	
				TALLY	17/17	16/16	

PPM, (mg/m ³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	, ()	, ()	, ()	, ()	, ()
AEGL 2	300 200, ()	200, ()	160, ()	100, ()	50, ()
AEGL 3	, ()	, ()	, ()	, ()	, ()

AEGL 1 Motion: _____

Second: _____

AEGL 2 Motion: Hinz

Second: Rodgers

AEGL 3 Motion: Hornshaw

Second: Hinz

Approved by Chair: [Signature]

DFO: Paul S. Todin Date: 3/7/03

* Do not develop LOA for carbon disulfide since the range of impurities cause 10³ range in odor detection.

Appendix I

NAC/AEGL Meeting 28: March 7-8, 2003

Chemical: **FORMALDEHYDE**

CAS Reg. No.:

50-00-0

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	N Y	F	Y Y	Nancy Kim	N Y	Y	Y Y
Steven Barbee	Y N	Y	Y Y	Loren Koller	Y N	Y	Y Y
Lynn Beasley	A A	A	A A	Glenn Leach	A A	A	A A
David Belluck	A A	A	A A	Mark McClanahan	Y N	Y	Y N
Robert Benson	P Y	Y	Y Y	John Morawetz	N Y	N	Y Y
Jonathan Borak	A A	A	A A	Richard Niemeier	A A	A	A A
William Bress	N Y	Y	Y Y	Marinelle Payton	N Y	Y N	Y Y
George Cushmac	Y Y	Y	Y Y	Zarena Post	A A	A	A A
Al Dietz	A A	A	A A	George Rodgers	N Y	Y	Y Y
Ernest Falke	N Y	Y	Y Y	George Rusch, Chair	Y P	Y	Y Y
Larry Gephart	A A	A	A A	Robert Snyder	Y Y	Y	Y Y
John Hinz	Y N	Y	Y Y	Thomas Sobotka	A A	A	A A
Jim Holler	Y Y	A Y	Y Y	Kenneth Still	A A	A	A A
Thomas Hornshaw	N Y	P	Y Y	Richard Thomas	N Y	Y	Y Y
				TALLY	8/17	14/16	18/18 *17/18

PPM, (mg/m ³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	1, ()	1, ()	1, ()	1, ()	1, ()
AEGL 2	8/14, ()	8/14, ()	8/14, ()	8/14, ()	8/14, ()
AEGL 3	127, ()	88, ()	70, ()	35, ()	18, ()

AEGL 1 Motion:

Second:

AEGL 2 Motion:

Second:

AEGL 3 Motion:

Second:

Approved by Chair:

DFO:

Date: 3/7/03

Re-move with new set of numbers for n = 3.9
WITHDRAW ORIGINAL MOTION + * BALLOT.
withdrawing original motion + replace with 1A PPM

Appendix J

NAC/AEGL Meeting 28: March 7-8, 2003

Chemical: ACETONE

CAS Reg. No.: 67-64-1

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	Y Y	Y	Y	Nancy Kim	Y Y	Y	Y
Steven Barbee	Y Y	N	Y	Loren Koller	Y Y	Y	N
Lynn Beasley	A A	A	A	Glenn Leach	A A	A	A
David Belluck	A A	A	A	Mark McClanahan	Y Y	Y	N
Robert Benson	Y Y	Y	Y	John Morawetz	Y Y	Y	Y
Jonathan Borak	A A	A	A	Richard Niemeier	A A	A	A
William Bress	Y Y	Y	Y	Marinelle Payton	Y Y	Y	Y
George Cushmac	Y Y	Y	Y	Zarena Post	A A	A	A
Al Dietz	A A	A	A	George Rodgers	Y Y	Y	Y
Ernest Falke	Y Y	Y	Y	George Rusch, Chair	Y Y	Y	Y
Larry Gephart	A A	A	A	Robert Snyder	X Y	Y	Y
John Hinz	Y Y	Y	Y	Thomas Sobotka	A A	A	A
Jim Holler	Y Y	Y	Y	Kenneth Still	A A	A	A
Thomas Hornshaw	Y Y	Y	Y	Richard Thomas	Y Y	Y	Y
				TALLY	14/15	15/16	16/16

PPM, (mg/m ³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	200 , ()	200 , ()	200 , ()	200 , ()	200 , ()
AEGL 2	9300 , ()	4900 , ()	3200 , ()	1400 , ()	950 , ()
AEGL 3	16000 , ()	8600 , ()	5700 , ()	2500 , ()	1700 , ()

* 16,000 ppm * > 50% LEL

D > 10% LEL

26,000 ppm

AEGL 1 Motion: N. Kim

Second: T. Hornshaw, J. Hinz, B. Bress

AEGL 2 Motion: R. Thomas

Second: J. Hinz

AEGL 3 Motion: Jim Hinz

Second: Tom Hornshaw

Approved by Chair: [Signature]

DFO: [Signature] Date: 3/8/03

2 MOVE R. THOMAS: LOA = 165 ppm
SECOND J. HINZ 170 ppm

Appendix K

NAC/AEGL Meeting 28: March 7-8, 2003

Chemical: HYDROGEN BROMIDE

CAS Reg. No.:

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	Y	P	Y	Nancy Kim	Y	Y	Y
Steven Barbee	Y	Y	Y	Loren Koller	Y	Y	Y
Lynn Beasley	A	A	A	Glenn Leach	A	A	A
David Belluck	A	A	A	Mark McClanahan	Y	Y	Y
Robert Benson	P	Y	Y	John Morawetz	Y	P	P
Jonathan Borak	A	A	A	Richard Niemeier	A	A	A
William Bress	Y	Y	Y	Marinelle Payton	Y	Y	Y
George Cushmac	Y	Y	Y	Zarena Post	A	A	A
Al Dietz	A	A	A	George Rodgers	A	A	A
Ernest Falke	Y	Y	Y	George Rusch, Chair	Y	Y	Y
Larry Gephart	A	A	A	Robert Snyder	Y	Y	Y
John Hinz	Y	Y	Y	Thomas Sobotka	A	A	A
Jim Holler	Y	Y	Y	Kenneth Still	A	A	A
Thomas Hornshaw	Y	Y	Y	Richard Thomas	Y	Y	Y
				TALLY	16/16	15/15	16/16

PPM, (mg/m ³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	1 , ()	1 , ()	1 , ()	1 , ()	1 , ()
AEGL 2	100 , ()	43 , ()	22 , ()	11 , ()	11 , ()
AEGL 3	740 , ()	250 , ()	120 , ()	31 , ()	31 , ()

AEGL 1 Motion: Hinz Second: Kim

AEGL 2 Motion: McClanahan Second: Kim

AEGL 3 Motion: Ernest Falke Second: Hinz

Approved by Chair: Geoff H. R. H. DFO: Paul S. Thi Date: 3/8/03

Appendix L

NAC/AEGL Meeting 28: March 7-8, 2003

Chemical: TITANIUM TETRACHLORIDE CAS Reg. No.: 7550-45-0

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	Y	Y	Y	Nancy Kim	Y	Y	Y
Steven Barbee	Y	Y	Y	Loren Koller	Y	Y	Y
Lynn Beasley	A	A	A	Glenn Leach	A	A	A
David Belluck	A	A	A	Mark McClanahan	A	Y	Y
Robert Benson	Y	Y	Y	John Morawetz	Y	Y	Y
Jonathan Borak	A	A	A	Richard Niemeier	A	A	A
William Bress	Y	Y	Y	Marinelle Payton	Y	Y	Y
George Cushmac	Y	Y	Y	Zarena Post	A	A	A
Al Dietz	A	A	A	George Rodgers	A	A	A
Ernest Falke	Y	Y	Y	George Rusch, Chair	Y	Y	Y
Larry Gephart	A	A	A	Robert Snyder	Y	Y	Y
John Hinz	Y	Y	Y	Thomas Sobotka	A	A	A
Jim Holler	Y	Y	Y	Kenneth Still	A	A	A
Thomas Hornshaw	Y	Y	Y	Richard Thomas	Y	Y	Y
				TALLY	16/16	17/17	17/17

PPM, (mg/m ³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	0.070, ()	0.070, ()	0.070, ()	0.070, ()	0.070, ()
AEGL 2	2.2, ()	2.2, ()	1.0, ()	0.21, ()	0.094, ()
AEGL 3	38, ()	13, ()	5.7, ()	2.0, ()	0.91, ()

AEGL 1 Motion: Koller Second: Thomas

AEGL 2 Motion: Koller Second: Thomas

AEGL 3 Motion: Koller Second: Thomas

Approved by Chair: [Signature] DFO: Paul S. Volin Date: 3/8/03